University of Canterbury

Department of Mathematics and Statistics

Cell-population growth modelling and nonlocal differential equations

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Abstract

Aspects of the asymptotic behaviour of cell-growth models described by partial differential equations, and systems of partial differential equations, are considered. The models considered describe the evolution of the size-distribution or age-distribution of a population of cells undergoing growth and division.

First, the relationship between the behaviour, with and without dispersion, of a single-compartment size-distribution model of cell-growth with fixed-size cell division (where cells can only divide at a single, critical size) is considered. In this model dispersion accounts for stochastic variation in the growth process of each individual cell.

Existence, uniqueness and the asymptotic stability of the solution is shown for a size-distribution model of cell-growth with dispersion and fixed-size cell division. The conditions for the analysis to hold for a more general class of division behaviours are also discussed.

A class of nonlocal ordinary differential equations is studied, which contains as a subset the nonlocal ordinary differential equations describing the steady size-distributions of a single-compartment model of cell-growth. Existence of solutions to these equations is found to be implied by the existence of 'upper' and 'lower' solutions, which also provide bounds for the solution.

A multi-compartment, age-distribution model of cell-growth is studied, which describes the evolution of the age-distribution of cells in different phases of cell-growth. The stability of the model when periodic solutions exist is examined. Sufficient conditions are given for the existence of stable steady age-distributions, as well as for stable periodic solutions.

Finally, a multi-compartment age-size distribution model of cell-growth is studied, which describes the evolution of the age-size distribution of cells in different phases of cell-growth. Sufficient conditions are given for the existence of steady age-size distributions. An outline of the analysis required to prove stability of the steady age-size distributions of the model is also given. The analysis is based on ideas introduced in the previous chapters.

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List of submitted papers

Most of the material in Chapter 2 appears in the paper "On a functional equation model of transient cell growth", published in *Mathematical Medicine and Biology*, volume 22, 2005 (pages 371-390) [8]. This work was co-authored with G.C. Wake and D.J.N. Wall.

Much of the material in Chapter 3 appears in the paper "On the stability of steady size-distributions for a cell-growth process with dispersion", submitted to the *Journal of Mathematical Analysis and Applications*. This work was co-authored with G.C. Wake and D.J.N. Wall.

Most of Chapter 4 appears in the paper "Existence theorems for a class of nonlocal differential equations", published in the *Journal of Mathematical Analysis and Applications*, volume 322, 2006 (pages 1168-1187) [7].

Contents

Glossary

Function Spaces

$C(U)$	:	Continuous functions from some region $U \subset \mathbb{R}^n$, $n \geq 1$ into $\mathbb{R}$.
$C[0,\infty)$, $C[a,b]$	:	As above on the intervals $[0,\infty)$, $[a,b]$.
$C^k(U)$, $C^k[0,\infty)$, $C^k[a,b]$	:	k-times continuously differentiable real functions on various domains.
$C_{per}[0,T]$	:	Used in Chapter 5, Section 5.6. $f(t) \in C_{per}[0,T]$ if and only if $f \in C(-\infty,\infty)$ and f is T-periodic. Any function $f \in C_{per}[0,T]$ can be identified with a function $g \in C[0,T]$ with $g(0) = g(T)$.
$L^\infty(U)$, $L^1[0,\infty)$, $L^2[a,b]$	:	Lebesgue function spaces.
$W^{a,b}(U)$	:	The Sobolev space of functions in $L^b(U)$ whose derivatives up to order a are also in $L^b(U)$.
CD, $CD(J)$, $CD[a,b]$	:	Definition from Chapter 3, Section 3.4: Let J be some interval with interior J_I and let $l > 0$ and $\alpha > 1$ be given. We define the set $CD(J)$ as follows: $f(x,t) \in CD(J)$ if and only if $f(x,t)$ is continuous for $x \geq 0$ and $t \in J$, $f_t(x,t)$ is continuous for all $x \geq 0$ and $t \in J_I$; and $f_x(x,t)$, $f_{xx}(x,t)$ are continuous for all $0 \leq x \neq l, l/\alpha$ and $t \in J_I$. Given the importance of $CD[0,\infty)$, we also define $CD = CD[0,\infty)$.

Abbreviations

SSD	:	Steady Size-Distribution.
SASD	:	Steady Age-Size-Distribution.

Cell-growth model terms

Variable Name	Description	Dimensions
x	Cell size	$[x] = [\text{size}]$
τ	Cell age	$[\tau] = [\text{time}]$
t	Time	$[t] = [\text{time}]$
$n(x,t)$	Density of cells at size x	$1/[x]$
$n(x,\tau,t)$	Density of cells at size x and age τ	$1/[x][\tau]$
g	Growth rate	$[g] = [x]/[t]$
D	Dispersion rate	$[D] = [x]^2/[t]$
B	Cell division rate	$[B] = 1/[t]$
μ, μ_{G_1}, μ_S, μ_{G_2}	Cell death rate; death rates in various phases	$[\mu] = 1/[t]$
k_{G_1}, k_S, k_{G_2}	Cell transfer rate from various phases	$[k_{G_1}] = [k_S] = [k_{G_2}] = 1/[t]$

In the thesis, the dimensions of the model parameters are not mentioned. The dimensions are listed in the table above in case the reader is interested.

Chapter 1

Introduction

1.1 The cell cycle

At the simplest level, the cell-cycle is a process whereby a cell undergoes growth for a period of time and then divides into two daughter cells; each of the daughter cells grows and divides in the same way, and so on. This is represented in Figure 1.1. We consider a cell to be growing if its size is increasing with time. However, depending on what we consider to be the cells 'size' the cell might grow at different rates or not at all. Consider the case of the cell-cycle for eukaryotic cells

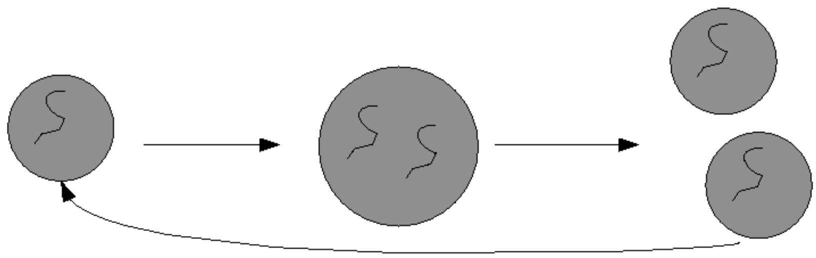


Figure 1.1: A simple diagram of the cell cycle showing a cell which doubles in size and then divides into two daughter cells.

if we take the size of a cell to be its DNA content:

The cell cycle for eukaryotic cells (cells with genetic material contained in a nucleus) is divided into four phases: G_1-, S-, G_2- and M-phase [51, 41, 50], occurring in that order. (For a simple introduction on the eukaryotic cell-growth cycle see [57].) The DNA content of any given cell only changes during S-phase (for 'DNA Synthesis'). Thus, if we identify the size of the cell as DNA content, a cell does not grow at all except during S-phase (although its mass or volume may

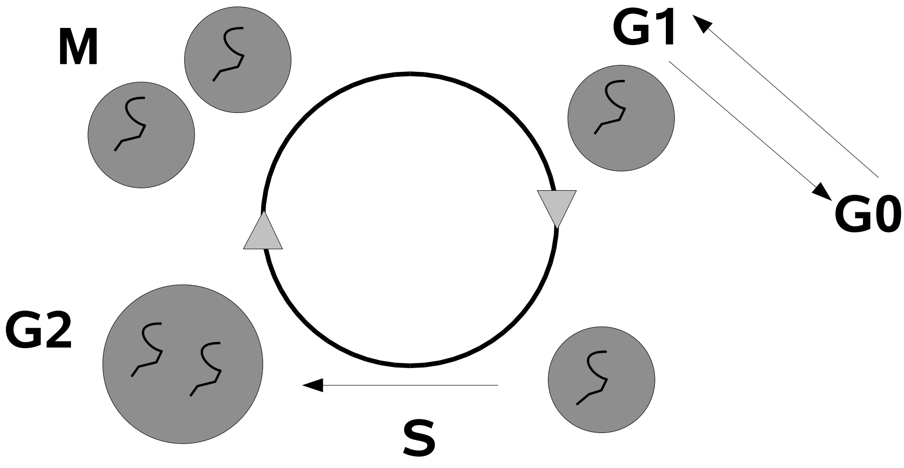


Figure 1.2: A diagram showing the phases of the cell-growth cycle in eukaryotic cells. DNA content only changes in the S-phase of cell growth.

change outside of S-phase). During the 'gap' phases G_1 and G_2 no change in DNA content takes place. During M phase (for 'Mitosis'), the cell divides into two daughter cells, each with an equal complement of DNA. The phases G_1, G_2 and S are collectively referred to as *interphase*, the time between one the completion of cell-division and the start of the next division [50].

Cells may be removed from the cell division process for an indefinite period in a state known as *senescence* or *quiescence* (sometimes referred to as G_0-phase). Cells in this state are still viable, but do not grow or divide. A cell may remain in senescence for up to a number of years before returning to the cell division cycle; for example, Liver cells will not usually grow or divide if unperturbed but will start grow and divide when the liver is damaged [51].

Cell-cycle time varies between organisms and cell types, and even within a population of cells, the cell-cycle time may show some significant variation. Cleaver ([18], Chapter 4, Section 9) cites several examples from the literature of different cell-types and their measured times in each phase. A few examples are given in Table 1.1. For more examples, and references see [18].

1.2 Modelling the growth of a cell population

The cell-growth models considered in the present work attempt to express rules for the evolution of the size-distribution or age-distribution of a cell-population (or, in Chapter 6, the age-distribution and age-size distribution respectively). That is, the models express rules governing how many

Cell Type	Time in phase (hrs)				
	G_1	S	G_2	M	Total time
Human Fibroblast	2.5	11.5	4.5	-	18.5
Human Skin	11.2	5.4	3.9	1.2	21.7
Onion Root Tip	10	7	3	5	25
Rat Liver (1 week old)	5	7	1.5	0.3	13.8
Rat Liver (3 weeks old)	9	9	1.8	1.7	21.5
Rat Liver (8 weeks old)	28	16	1.8	1.7	47.5

Table 1.1: Examples of the time spent in different phases of the cell-cycle for various cell types (taken from [18]). The cycle times for human fibroblast and human skin cells are for cells *in vitro*, while the other times are for cells *in vivo*. The entry for human fibroblast cells does not have a time for M-phase because it is difficult to determine when M-phase begins and ends [50, Chapter 4]. M-phase in this case is included in the times for G_1- and G_2-phase.

cells in the population are of any given size (or age) at any given time. As mentioned above, different measurements could be used for the 'size' of a cell. For example volume, radius, mass or DNA content. Considering cell-size as DNA content, at least in eukaryotes, is more suited to a multi-compartment model for cell-growth including G_1-, S-, G_2- and M-phases, since the only changes in the 'size' of a cell will occur during S-phase.

DNA content in cells may be measured by flow cytometry [46, 65, 64, 63]. Cells are stained with a fluorescent dye which is attracted to the DNA in the cells. They are then passed through a laser one by one. The laser excites the fluorescent dye within the cells, which fluoresce a certain colour. The fluorescence of each cell is used as a measure of how much DNA is contained within each cell. Data from the whole population of cells can then be used to create a DNA histogram which, with a large enough sample size, roughly approximates a continuous density distribution of cells at any given size.

There are two approaches taken in this thesis to modelling the evolution in time of the distribution of a cell-population structured by size or age. The first is to use a single-compartment model with parameters for growth, death and division rates as well as for dispersion due to the stochastic nature of the cell-growth process (see Section 1.5, and especially subsection 1.5.3). This approach matches the simple diagram from Figure 1.1.

The second approach is to separate the model into different compartments, corresponding to different phases of the cell cycle, represented in Figure 1.2. In this case the S-phase compartment of the model is similar to the single-compartment model, while the G_1- and G_2-phase compartments work as stochastic delays. If DNA content is considered as cell size then the multi-compartment model is more appropriate, since DNA content only changes in the S-phase of the cell cycle. The one-compartment model, on the other hand, is more suited to modelling the actual physical size of a cell, which can change in G_1-, G_2- and S-phase. However, the one-compartment model may still be useful for modelling the evolution of the DNA-distribution of some cell types, since we can see from Figure 1.4 that while a population of *E-coli* is undergoing logarithmic growth, the shape of its DNA distribution is similar to that of the one compartment model with fixed-size cell division (See [6] and Chapter 3). This sort of distribution also occurs in some mammalian cell types in suspension cultures [2].

The motivation for analysing the cell growth models described below is both mathematical and biological. Models similar to the those studied in Chapters 5 (see [15] and [61]) and 6 (see [3] and [5]) have been considered in the context of modelling tumour cell-growth and the response to chemotherapy. Moreover, although the single-compartment model described in Section 1.4 may have less practical use, the mathematical ideas used in studying this equation may be useful in studying multi-compartment models. Indeed, in Chapter 6 it is seen that using ideas introduced in Chapter 3, it should be possible to prove the stability of the model (time constraints in writing this thesis have prevented the analysis in Chapter 6 from being carried through fully).

1.3 Steady Size-Distributions

Steady size-distributions, or SSDs, occur when the size-distribution of a cell-population retains a constant shape while the overall number of cells in the population may be growing or decaying. Steady size-distributions are merely the part of a separable solution to a given model which depends on size only. For instance, suppose that $n(x,t)$ models the density of cells of size x at time t and suppose, further, that $n(x,t) = N(t)y(x)$ for some function N of time and y of the size variable x. We call the function $y(x)$, which depends only on size, a steady size-distribution. In Chapter 5, we deal with steady age-distributions. These are defined in the same way as steady size-distributions, but instead of size a different structuring variable (age) is used. In Chapter 6 we deal with steady age-size distributions, which are again similarly defined to steady size-distributions with the addition of a structuring variable for age.

SSDs are observed to occur in physical cell populations [14, 2, 65, 4, 3], so it is desirable that SSD solutions exist for the cell model under investigation, that at least one is an attractor and that the SSDs match the observations from the population of cells being modelled. An example of a population of cells (Ovarian cancer cells) *in vitro* tending to an SSD is given in Figure 1.3. Another example is given in Figure 1.4, where two SSDs for a culture of *E-Coli* are shown: one associated with a cell-population growing exponentially. The other associated with a steady cell-population. In [2], volume distributions were measured for various mammalian cells in suspension cultures (where cells are suspended in a medium rather than adhering to a surface). Stable distributions similar to that shown in Figure 1.4 were found to arise often among the cell types studied.

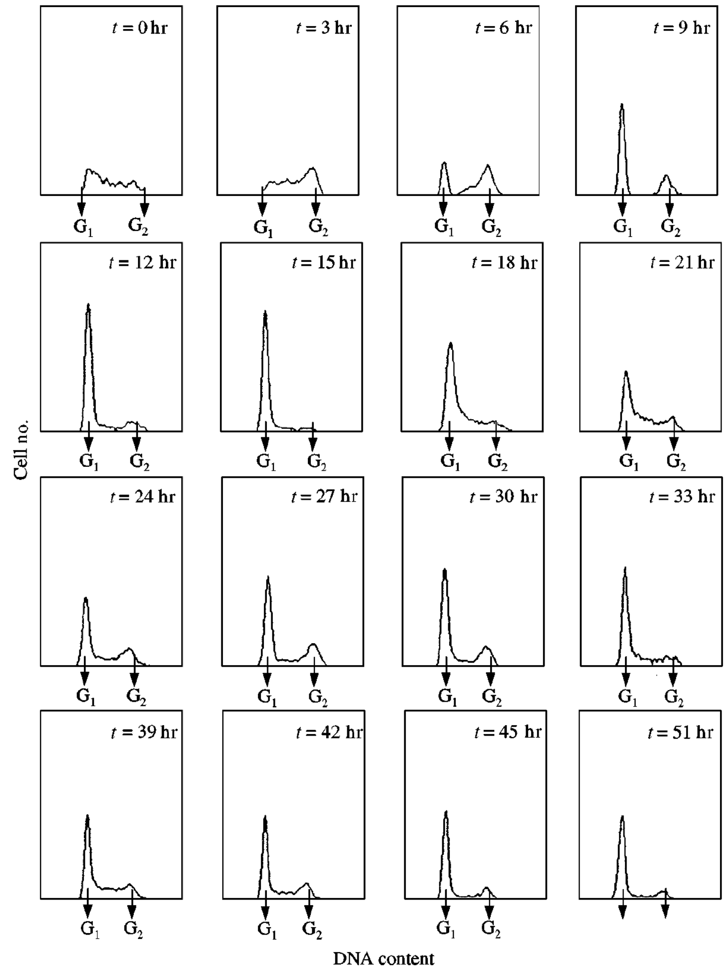


Figure 1.3: A figure, taken from [14], showing the evolution in time of the DNA size-distribution of a population of ovarian cancer cells. Clearly an SSD develops, with peaks corresponding to the G_1- and G_2- phases.

SSD behaviour is also known as *Balanced Exponential Growth* (BEG) or *Asynchronous Exponential Growth* (AEG). The term asynchronous comes from the fact that while the size-distribution

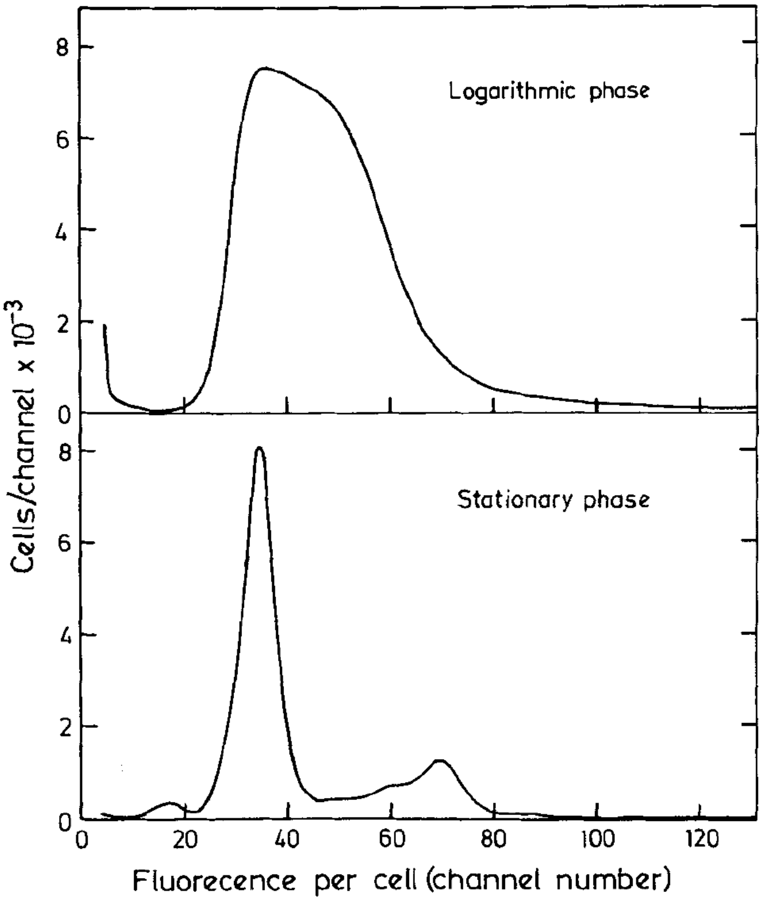


Figure 1.4: Steady DNA Distributions from [65] for a culture of *E-Coli* cells. The upper shape arises while the overall cell-population is growing exponentially, while the lower shape arises when the growth in the overall number of cells has stabilised. The horizontal axis is labelled 'fluorescence per cell' because this is how DNA content is measured in flow cytometry.

of the population is increasing at the same exponential rate at all sizes, the individual cells in the population may be at different parts of the cell cycle (growing asynchronously).

There are three key questions regarding SSD behaviour in a cell-growth model: Do SSD solutions exist? What is the form of the SSD(s)? Are the SSDs (global) attractors? This thesis is mainly concerned with addressing these questions.

1.4 The single-compartment model

The single-compartment model studied here is, in its most general form,

$$\begin{aligned} \frac{\partial}{\partial t}n(x,t) &= \frac{\partial^2}{\partial x^2}\left(D(x,t)n(x,t)\right) - \frac{\partial}{\partial x}\left(g(x,t)n(x,t)\right) - \mu(x,t)n(x,t) \\ &\quad + \alpha^2 B(\alpha x,t)n(\alpha x,t) - B(x,t)n(x,t), \end{aligned} \tag{1.4.1}$$

where $n(x,t)$ is the density of cells of size x and time t; thus to find the number of cells between size a and b, $0 \leq a < b$, one must integrate $n(x,t)$ with respect to x between $x = a$ to $x = b$. The coefficients in (1.4.1) are shown as functions of x and t, but generally they will be considered either as constants or functions of x alone. D is a dispersion coefficient which models white-noise in the growth-process of each individual cell (see [53], [25] and Section 1.5.3 for an explanation of the relationship between classical dispersion and stochastic diffusion); g is the growth-rate at (x,t) or, more appropriately, the mean growth rate, given that the growth of cells is considered here to be a stochastic process; μ is the death rate and B is the cell-division rate. The constant $\alpha > 1$ represents how many daughter cells are produced at the division of a parent cell. Biological cells divide into two daughter cells, so $\alpha = 2$ is a realistic assumption. However, other values for α may be of mathematical interest even if they are not biologically realistic.

For example, out of mathematical curiosity we may be interested in how the model behaves for $\alpha = 1.4$. This would correspond to an aggregate of cells (say 5 cells) producing an additional 0.4 times their own number in daughter cells (2, when there are 5 parent cells), with each of the parent cells contributing an equal quantity of DNA to the production of the daughter cells. This would, however, be an unusual occurrance.

Equation (1.4.1) is supplemented with the boundary conditions

$$\lim_{x\to\infty} n(x,t) = 0; \tag{1.4.2}$$

$$\lim_{x\to\infty} \frac{\partial}{\partial x} n(x,t) = 0; \tag{1.4.3}$$

$$\left[\frac{\partial}{\partial x}\left(D(x,t)n(x,t)\right) - g(x,t)n(x,t)\right]_{x=0} = 0. \tag{1.4.4}$$

The conditions at $x = \infty$ ensure regularity of the solution and make the problem of finding a solution to (1.4.1) simpler. If we are interested in the transient behaviour of the model, rather than the existence or the form of the SSDs, we also add the initial condition

$$n(x,0) = n_0(x), \qquad x \geq 0. \tag{1.4.5}$$

We expect that there will always be a finite number of cells and that their size-distribution will be bounded at any time $t \geq 0$.

The single-compartment model above essentially neglects the phases G_1, G_2 and M. Cell division is instantaneous, with no pause in growth at any stage in the cell-cycle.

A model of the age-size distribution of cells growing and dividing was formulated in 1967 by Bell and Anderson [10]. In [9], the existence of steady age-size distributions to the model in [10] was proved under the conditions of fixed-age cell division (all cells divide instantly upon reaching a fixed age τ_0). Under certain conditions local stability, but not global stability, was shown. The fact that the division of cells occurs at a fixed age without any dispersive mechanism in that case is a similar situation to the fixed-size division case, where $B(x) = b\delta(x-l)$, of the singel-compartment model above with $D = 0$. This case is dealt with in Chapter 1.

It should also be mentioned that the single compartment model above describes *symmetric* cell-division. That is, each cell division results in the formation of daughter cells of equal size. The case where the two daughter cells may be of unequal size is known as *asymmetric* cell division. The governing differential equation in this case may be given by

$$\begin{aligned}\frac{\partial}{\partial t}n(x,t) &= \frac{\partial^2}{\partial x^2}\left(D(x,t)n(x,t)\right) - \frac{\partial}{\partial x}\left(g(x,t)n(x,t)\right) - \mu(x,t)n(x,t) \\ &\quad + \int_x^\infty b(x,y)n(y,t)dy - B(x,t)n(x,t).\end{aligned}$$

where $b(x,y)$ represents the rate of production of cells with size x from cells of size y. The condition that a single cell divides into α daughter cells translates into

$$\int_0^y b(x,y)\ dx = \alpha B(y).$$

In words, the above equation states that the rate of production of daughter cells of any size from cells of size x (the integral term on the left hand side) must be α times the rate of loss of cells from size x due to cell division. In the case where a cell divides into two daughter cells, we should also have $b(y/2+x,y) = b(y/2-x,y)$ for all $x \leq y/2$. This represents the fact that whenever a cell of size $y/2+x$ is produced on division of a cell of size y, the other daughter cell must have size $y/2-x$. See [33] for a study of a model with asymmetric cell division (albeit formulated in a different way to the above) which also includes the effect of nutrient availability on the growth of cells. The cell-growth model in [49] is also formulated using a division kernel $b(x,y)$ before examining the special case $b(x,y) = 2B(y)\delta(y/2-x)$ (symmetric cell-division with $\alpha = 2$).

In a more general sense, the single compartment model above is a fragmentation equation with an added growth process. A general fragmentation equation, describing the size-distribution of particles (for instance, spray droplets), will behave like asymmetric cell-division described above, with a fragmentation kernel $b(x,y)$, but the particles will not naturally grow in size. In pure fragmentation models, particles can only decrease in size. The special solutions of interest in this case are of the form:

$$n(x,t) = t^{2\nu}g(t^\nu x)$$

and are known as self-similar solutions [22].

Previous work on the asymptotic behaviour of cell-growth models has in general not included a dispersion term Dn_{xx} to account for stochastic variability in the growth process of each individual cell. Here however, we are usually interested in the case where $D > 0$.

A good reference on the topic of physiologically structured populations is [47]. Two examples of papers on the mathematical properties of variations of the above model with $D = 0$ are [34, 35].

[48] gives results for a class of models which show asymptotic stability to a steady age or size distribution if such a steady distribution exist. In [49] these results are described in more detail and the existence of steady age and size distributions is considered as well. When size-distributions are considered the models lack any second order derivative n_{xx}. In [55] the rate of convergence to steady size-distributions is found for the single-compartment model with $D = 0$, constant g and μ (in fact, zero μ, but the problems are equivalent), and division function $B(x)$ close to a constant.

In [20] it is proved that convergence to a steady size-distribution occurs in the single compartment model with $D = 0$ and

$$\int_0^x B(\xi)\ d\xi \to \infty$$

as $x \to 1^-$, as long as the growth-rate function satisfies the condition $g(2x) < 2g(x)$.

In [29] the behaviour of 'mild' solutions to a delay differential equation model related to the model studied here is examined. The cells were assumed to be either in a normal (growth) phase or a division phase taking a fixed amount of time r. The model was essentially a generalisation of that in [20]. Given an initial condition on $\{(t, x) : t \in [-r, 0],\ x \in [x_0, 1]\}$, where x_0 is the least possible cell size, it was shown that the solution of the model tends to an SSD as $t \to \infty$.

An example study of an age-size distribution model can be found in Chapter 5 of [47], which deals with the stability of a single-compartment, age-size distribution model of cell division without dispersion. It is shown that the model tends to a steady age-size distribution with exponentially decreasing error.

Tucker and Zimmerman [67] studied a quite general one-compartment non-linear population growth model, where the population is structured by age and an arbitrary number of other structuring variables (for example size and DNA content in a cell-growth context). The domain of the structuring variables other than age is assumed to be compact and other assumptions are made regarding smoothness of coefficients and Lipschitz continuity of the initial conditions. A result is presented which gives sufficient conditions for the steady states of the model to be locally asymptotically stable. An example is given wherein the trivial solution is locally asymptotically stable if the death rate of a population is high enough.

None of the above references include dispersion in their cell-growth models, which is present in this thesis except in Chapter 2, and Chapter 5 where we deal with a multi-compartment age-distribution model of cell-growth.

1.5 Derivation of the single-compartment model

Here a simplistic derivation of (1.4.1) is given, with constant coefficients g, D and μ. We shall then discuss the relationship of the single-compartment model with stochastic differential equations and the Fokker-Planck equation.

1.5.1 The discrete system

Consider a number of cells either growing or shrinking by Δx in each discrete time interval of Δt. Cells of size x divide at any given instant of time with a probability of $B(x)\Delta t$ into α daughter cells of size x/α.

Let the probability that a cell grows at any time-step be p and the probability that a cell shrinks be $q = 1 - p$. Further, let $n(x, t)$ be the density function for cells of size x at time t. Then the discrete system may be expressed as,

$$\int_{x-\Delta x/2}^{x+\Delta x/2} n(\xi, t)\, d\xi = p \int_{x-3\Delta x/2}^{x-\Delta x/2} n(\xi, t - \Delta t)(1 - B(\xi)\Delta t)\, d\xi \tag{1.5.1}$$

$$+q \int_{x+\Delta x/2}^{x+3\Delta x/2} n(\xi, t - \Delta t)(1 - B(\xi)\Delta t)\, d\xi \tag{1.5.2}$$

$$+\alpha \int_{\alpha x-\alpha\Delta x/2}^{\alpha x+\alpha\Delta x/2} B(\xi)(\Delta t)n(\xi, t - \Delta t)\, d\xi, \qquad x >> \Delta x. \tag{1.5.3}$$

Assuming n has only isolated points of discontinuity, then as $\Delta x \to 0$ we may approximate this as

$$n(x, t) = pn(x - \Delta x, t - \Delta t)(1 - B(x - \Delta x)\Delta t) + qn(x + \Delta x, t - \Delta t)(1 - B(x + \Delta x)\Delta t)$$
$$+ \alpha^2 B(\alpha x)(\Delta t)n(\alpha x, t - \Delta t),$$

for almost every $x >> \Delta x$.

1.5.2 The continuous limit

Consider now the expression for $n(x, t)$ when $x > 0$. Assuming that Δx and Δt are small in relation to x and t, and further that the terms on the right hand side of the equation can be expanded in Taylor series around x and t, we find:

$$\begin{aligned} n(x-\Delta x, t-\Delta t) &= n(x,t) - \Delta x \frac{\partial n}{\partial x} - \Delta t \frac{\partial n}{\partial t} + \frac{(\Delta x)^2}{2}\frac{\partial^2 n}{\partial x^2} + \dots, \\ n(x+\Delta x, t-\Delta t) &= n(x,t) + \Delta x \frac{\partial n}{\partial x} - \Delta t \frac{\partial n}{\partial t} + \frac{(\Delta x)^2}{2}\frac{\partial^2 n}{\partial x^2} + \dots, \\ n(x, t-\Delta t) &= n(x,t) - \Delta t \frac{\partial n}{\partial t} + \dots . \end{aligned}$$

Each partial derivative in the above expression is calculated at x and t. Substituting the above into the expression for $n(x,t)$, letting $\varepsilon = p - q$ and using the fact that $p + q = 1$, we find

$$n_t = -[pB(x-\Delta x) + qB(x+\Delta x)]n(x,t) + \alpha^2 B(\alpha x)n(\alpha x, t) - \frac{(\Delta x)\varepsilon}{\Delta t} n_x + \frac{(\Delta x)^2}{2\Delta t} n_{xx} + ...,$$

with the remaining higher order terms all having $(\Delta t)^k(\Delta x)^j$ as a factor, where $k, j \geq 0$ and $k + j \geq 1$. Consider now the limiting process as the parameters $\Delta t, \Delta x$ and ε tend to zero. Suppose also that as $\Delta t \to 0$, the parameters Δx and ε are $O(\sqrt{\Delta t})$. Then let,

$$g = \lim_{\Delta x, \Delta t, \varepsilon \to 0} \frac{(\Delta x)\varepsilon}{\Delta t}, \qquad D = \lim_{\Delta x, \Delta t \to 0} \frac{(\Delta x)^2}{2\Delta t}.$$

Note that the higher order terms vanish as $\Delta t, \Delta x, \varepsilon \to 0$. Thus we obtain

$$n_t = -gn_x + Dn_{xx} - B(x)n(x,t) + \alpha^2 B(\alpha x)n(\alpha x, t), \qquad x > 0, \tag{1.5.4}$$

as the continuous limit of the discrete process described above. This is equivalent to (1.4.1) with death rate $\mu = 0$ and constant D and g. To include a positive death rate μ into the equation, it is required to multiply the right-hand side of (1.5.1) by $(1 - \mu\Delta t)$ to describe a proportion $(\mu\Delta t)$ of cells dying at each time step. This results in an extra term, $-\mu n(x,t)$, appearing on the right hand side of Equation (1.5.4).

A similar derivation to the one shown above, without the division function $B(x)$, can be found in [54].

1.5.3 Relationship of the single-compartment model to stochastic differential equations and the Fokker-Planck equation

The single-compartment model given in (1.4.1) can be considered as a modified Fokker-Planck equation. The Fokker-Planck equation describes the probability density function of the position of a particle undergoing deterministic drift with added stochastic diffusion. Restricting mathematical expressions to the one-dimensional case (since effectively we are working in only one spatial dimension in the model (1.4.1)), the position of such a particle is described by the Ito stochastic differential equation [53, 25]:

$$dx(t) = g(x(t), t)dt + \sigma(x(t), t)dW_t,$$

where W_t is known as a Weiner process. By itself, $W_t - W_s$ is a gaussian distribution with mean zero and standard deviation $t - s$. The addition of this process into the differential equation for x means that we can't be certain what value x will attain at a given time t. However, we can find a probability density function describing how likely it is that x is in any given range at time t. Let $f(x,t)$ denote this probability function. Then the evolution of $f(x,t)$ in time is described by the Fokker-Planck equation [25]:

$$\frac{\partial}{\partial t} f(x,t) = -\frac{\partial}{\partial x}(g(x,t)f(x,t)) + \frac{\partial^2}{\partial x^2}(\sigma^2(x,t)f(x,t)). \tag{1.5.5}$$

Consider now the case where we have more than one particle in the system and assume that the number of particles is large. Without a mechanism to add or subtract particles from the system (such as cell-death or cell-division), we can multiply Equation (1.5.5) by the number of particles, N, in the system to obtain a differential equation describing the evolution of the density distribution of particles, $n(x,t)$, as time increases. The resulting equation is of exactly the same form as (1.5.5). We then let $D(x,t) = \sigma^2(x,t)$, subtract the loss due to cell division: $-B(x)n(x,t)$, and cell death: $-\mu(x,t)n(x,t)$, and add the gain due to cell division: $\alpha^2 B(\alpha x)n(\alpha x,t)$, to obtain Equation (1.4.1).

1.6 Multi-compartment models

Multi-compartment models for cell-growth are considered in Chapter 5 and 6. In Chapter 5 we investigate an age-distribution model (a simple version of that studied in [61]), while in Chapter 6, we investigate an age-size distribution model (based on the model in [3, 5]) of cell-growth over the phases G_1, S and G_2. The M-phase is absent from both models (or subsumed by the G_2 and G_1 phases) for mathematical simplicity. Adding a compartment for M-phase in either of the models in Chapters 5 and 6 should not change the behaviour of the models drastically.

The 'age' of any given cell is considered to be the time spent in the current phase of the cell cycle. When looking at the age-size distribution model, we consider DNA content to be the 'size' of a cell. Thus, changes in cell size only occur during S-phase.

In all phases cells age at a constant rate and either leave their current cell-growth phase by dying or transferring into the next phase of cell-growth. Cells move from one phase to another according to given transfer rates. Once a cell enters a new phase its age becomes zero. Its size is unchanged when moving from G_1 to S phase, but due to cell division occurring between G_2 and G_1 phases, new cells in the G_1-phase are half the size of cells leaving the G_2 phase.

The age-distribution multi-compartment model considered in Chapter 5 is described by:

$$\frac{\partial n(\tau,t)}{\partial t} + \frac{\partial n(\tau,t)}{\partial \tau} = -D_{out}(\tau,t)n(\tau,t); \qquad n(0,t) = \int_0^\infty D_{in}(\tau)n(\tau,t)\; d\tau,$$

where τ represents age, n is a vector valued function representing how many cells of age τ are in each phase at time t and D_{out} is a diagonal matrix representing the loss of cells from each phase due to death or transfer to another phase, and D_{in} is a matrix representing the contribution from each phase to every other phase. The model is described in more detail in Chapter 5.

The age-size distribution model considered in Chapter 6, is slightly more complicated. The phases G_1 and G_2 behave similarly to the G_1 and G_2 phases in the age-distribution model described above, since size does not change during those phases, whereas in S phase the cells grow in size as well as age. Similarly to the single-compartment model, we consider that the growth process of cells in S-phase is stochastic, so that the equation for cells in S-phase looks like:

$$S_t(x,\tau,t) + S_\tau(x,\tau,t) = DS_{xx}(x,\tau,t) - gS_x(x,\tau,t) - \mu_S S(x,\tau,t),$$

where μ_S is the (constant) death rate of cells in S-phase.

1.7 Outline of thesis

Chapter 2

We examine what happens to the single-compartment model from Section 1.4 when we have constant coefficients $\alpha > 1$, $g > 0$, $\mu \geq 0$, $D = 0$ and $B(x) = \delta(x - l)$. The behaviour of the model in this situation is related to the SSDs to the single compartment model with $B(x) = \delta(x - l)$ and D small (the SSDs are found in [6]). However, instead of tending to a steady size-distribution, periodic behaviour emerges with a bounding shape, which we call the 'hull', given by the limiting form of the SSDs for D non-zero as $D \to 0$.

We then let the growth rate vary with size, which changes the shape of the hull. It was thought that this shape would be similar to the shape of the SSDs for small D and the same growth-rate function. However, the SSDs for variable growth-rate $g(x)$ and $D > 0$ are not known and the problem of finding their form for general $g(x)$ seems difficult.

Most of the material in Chapter 2 appears in the paper "On a functional equation model of transient cell growth", published in *Mathematical Medicine and Biology*, volume 22, 2005 (pages 371-390) [8]. This work was co-authored with G.C. Wake and D.J.N. Wall.

Chapter 3

In this chapter we investigate the existence and stability of the transient solution to the single-compartment cell-growth model with constant coefficients $\alpha > 1$, D, $g > 0$, $\mu \geq 0$ and fixed-size cell division ($B(x) = b\delta(x-l)$, $l > 0$). The stability of SSD solutions to the model is proven using a 'generalised relative entropy functional' $\mathcal{H}$. The functional is non-negative and decreasing and so must converge to some value as $t \to \infty$. This information is then used to show that

$$n(x,t)e^{-\lambda t} \to ky(x)$$

in $L^1_{loc}(0,\infty)$ as $t \to \infty$, where λ is the eigenvalue associated with the SSD $y(x)$ and k is a constant depending on the initial conditions $n(x,0) = n_0(x)$. The approach used here follows [48, 49], but the analytical detail here is greater. The presence of dispersion in the model also provides a point of difference, and certain assumptions such as $n_0(x)$ being bounded by a constant multiple of $y(x)$ (which was used in [49]) are not needed here.

The analysis in this chapter could potentially apply to other division functions $B(x)$, different from $b\delta(x-l)$, and we try to outline the points that are required for the analysis to follow through in other cases at the end of Section 3.3.

Much of the material in Chapter 3 appears in the paper "On the stability of steady size-distributions for a cell-growth process with dispersion", submitted to the *Journal of Mathematical Analysis and Applications*. This work was co-authored with G.C. Wake and D.J.N. Wall.

Chapter 4

Here we investigate the existence of solutions to nonlocal differential equations of the form

$$y''(x) = f(x, y(x), y^*(x), y'(x)),$$

(supplemented by boundary conditions) where $y^*(x) = y \circ \lambda(x)$ for some function $\lambda(x)$. In the case of cell-division $\lambda(x) = \alpha x$. This problem relates to the question of existence of SSDs to the single-compartment model for different sets of parameters. Assuming the existence of 'upper' and 'lower' solutions ψ and ϕ to the problem, which satisfy the differential inequalities

$$\psi(x) \leq f(x, \psi(x), \psi^*(x), \psi'(x)), \qquad \phi(x) \leq f(x, \phi(x), \phi^*(x), \phi'(x)),$$

it can be shown that a solution exists. Thus, the problem of finding an exact solution to the differential equation is reduced to finding two functions satisfying differing differential inequalities.

An example of the use of upper and lower solutions is given in Section 4.6, for a problem related to the single-compartment model from Section 1.4 when $B(x) \equiv b > 0$.

The results are then extended to account for cases such as $y^*(x) = \int_0^\infty b(x,\xi)y(\xi)\ d\xi$, where the kernel b satisfies some assumptions.

Most of this chapter appears in the paper "Existence theorems for a class of nonlocal differential equations", published in the *Journal of Mathematical Analysis and Applications*, volume 322, 2006 (pages 1168-1187) [7].

Chapter 5

In this chapter, a multi-compartment age-distribution model of cell-growth is examined using a similar technique to that used in Chapter 3. The method is again from [48, 49], but here we apply it to a multi-compartment model. In [48, 49], the analysis is not done in much detail, so in this chapter more care is taken to show that various integrals converge and other such details. A stability result is given in Theorem 5.4.5 for periodic solutions of the model (assuming that a periodic solution exists).

It is then shown that steady age-distributions exist in some cases when the coefficients are independent of time (Theorem 5.5.3), and that when steady age-distributions exist, they are stable. This sort of analysis is repeated for the case when the coefficients of the model are periodic in time. The proof of existence of periodic solutions is quite complicated and relies on the Krein-Rutman theorem (Theorem 5.6.2), and a theorem from Kato [40] (Theorem 5.6.7).

Chapter 6

In this chapter we study a model based on that in [3]. Again it is a multi-compartment cell-growth model, but here we model the age-size distribution of cells in each phase of cell-growth. In the analysis we avoid shortcuts such as approximating zero flux boundary conditions by Dirichlet boundary conditions, or approximating the generalised Fourier series of a function by a finite sum. The analysis has not been carried out in full, but a framework has been laid in which (if the details are completed) we can prove analytically the stability of the steady age-size distributions of the model.

Chapter 2

Fixed-size cell division in the single-compartment model with no dispersion

2.1 Introduction

In this chapter an instance of the single compartment model from Section 1.4 with $D \equiv 0$ is studied. Most of the material in this chapter appears in [8].

The specific governing equation, studied here, for the size distribution $n(x,t)$ of a cell population, is given as

$$\frac{\partial}{\partial t}n(x,t) = -\frac{\partial}{\partial x}g(x)n(x,t) + \alpha^2 B(\alpha x)n(\alpha x,t) - B(x)n(x,t) - \mu(x)n(x,t), \quad t, x > 0. \tag{2.1.1}$$

where the coefficients of the model do not depend on t. Recall that $g(x)$ and $\mu(x)$ represent the growth rate and death rate respectively of cells of size x, and that $B(x)$ is the division rate of cells of size x. The functional equation (2.1.1) is supplemented by the side conditions

$$n(0,t) = 0, \qquad t > 0 \tag{2.1.2}$$

$$n(x,0) = n_0(x), \qquad x \geq 0, \tag{2.1.3}$$

For the sake of realism we are most interested in solutions where $n \geq 0$.

Further, we shall consider the case when cells may divide only at a fixed size $x = l$. Mathematically, we model fixed size division by a function of the form $B(x) = b\delta(x-l)$, where $b > 0$ is a constant and δ denotes the Dirac delta distribution. In this case the equation (2.1.1) becomes

(after moving all derivative terms to the left hand side)

$$\frac{\partial}{\partial t}n(x,t) + \frac{\partial}{\partial x}g(x)n(x,t) = \alpha b n(x,t)\delta(x - l/\alpha) - bn(x,t)\delta(x-l) - \mu(x)n(x,t). \tag{2.1.4}$$

We note that the continuity of $n(x,t)$ cannot be guaranteed at $x = l$ and therefore it may be that $\delta(x-l)n(x,t)$ is not properly defined. We henceforth specify $\delta(x-l)n(x,t)$ as denoting $\delta(x-l)n(l^-,t)$ (where $x = l^-$ is to denote the limit as $x \to l$ from below) observing in this case that cells above size l do not take part in the division process. Substituting this into (2.1.4) gives

$$\frac{\partial}{\partial t}n(x,t) + \frac{\partial}{\partial x}g(x)n(x,t) = \alpha b n(l^-,t)\delta(x - l/\alpha) - bn(l^-,t)\delta(x-l) - \mu(x)n(x,t). \tag{2.1.5}$$

We observe that it is also possible to use the limit from the right, so that we consider $\delta(x-l)n(x,t)$ to denote $\delta(x-l)n(l^+,t)$ instead. This yields similar results but we feel it is not as physically relevant as continuity from the left. The relationship between the two cases is discussed in Section 2.4.

Equation (2.1.5) is a special case of the equation which was examined in [6] (a reference which we henceforth denote by I). In I the SSDs of (2.1.5), with an added dispersion term Dn_{xx} on the right hand side, were studied.

It is shown here that when the dispersion term is removed from the model in I to obtain (2.1.5), the solution is in most cases discontinuous. However, it is further proved in this chapter that the hull (a bounding envelope, to be defined later) of the discontinuous solution is, under certain conditions, the SSD solution obtained in I as the dispersion tends to zero and furthermore is a global attractor (in the sense that, after periodic behaviour is removed, the shape of the solution will tend to that of the hull; see Section 2.3).

SSDs in I were found by assuming separable solutions of the form $n(x,t) = \mathcal{T}(t)y(x)$, to the single-compartment model from Equation (1.4.1), given in Chapter 1, with coefficients depending on x only ($y(x)$ in this case would then be an SSD). This leads to the equation

$$\frac{\mathcal{T}'(t)}{\mathcal{T}(t)} = \frac{(D(x)y(x))''}{y(x)} - \frac{(g(x)y(x))'}{y(x)} + \alpha^2\frac{B(\alpha x)y(\alpha x)}{y(x)} - (B(x)+\mu(x)) = \Lambda, \tag{2.1.6}$$

for some constant Λ. Immediately, the solution for $\mathcal{T}$ is found to be

$$\mathcal{T}(t) = \mathcal{T}_0 e^{\Lambda t}, \tag{2.1.7}$$

where $\mathcal{T}_0$ is a constant. The condition that $y(x)$ is a probability density function (that is $\int_0^\infty y(x)\,dx = 1$) leads to the following expression for Λ:

$$\Lambda = \int_0^\infty ((\alpha-1)B(x) - \mu(x))\,y(x)\,dx,$$

with the sign of Λ determining whether the number density function decays or grows exponentially in time. Letting $B(x) = b\delta(x - l)$ and the other coefficients be constant then gives a relationship between $y(l)$ and Λ:

$$\Lambda = (\alpha - 1)by(l) - \mu. \tag{2.1.8}$$

Sufficient conditions were then obtained for the existence of continuous SSDs. Existence of SSDs, however, does not tell us anything regarding their asymptotic stability. Here we show a SSD to be, in a sense, a global attractor.

In the present chapter we relate the solution to the initial value problem with $D = 0$ in (1.4.1) to the SSDs obtained in I. We show that the limiting shape of the SSDs in I as $D \to 0$ always appears in the solution for $D = 0$ regardless of the initial conditions, but not necessarily as an SSD. In Section 2.2 we restrict the analysis of the behaviour of the model to the case where the two coefficients g and μ are constant; this is an essential preliminary step before analysing the behaviour of the model for variable g. In Section 2.2.3 we show it is possible to express $n(x,t)$ as the solution to a retarded functional equation. In Section 2.2.4 (and in detail in Section 2.7) we discuss how the solutions to (2.1.5) grow or decay exponentially with time, while also exhibiting periodic behaviour. In Section 2.3 we show that (under certain conditions) the hull of the solution when $D = 0$ is equal to the limiting SSD from Ias $D \to 0$ with the requirement of continuity from the left. Finally, in Section 2.5 we find a general expression for the hull of $n(x,t)$ with variable growth rate $g = g(x)$. We often assume that $\alpha = 2$ in parts of the remainder of this chapter when the mathematics for general $\alpha > 1$ is more complicated.

2.2 Solution of the Differential Functional Equation

When $g > 0$ and $\mu \geq 0$ are constants, Equation (2.1.5) may be written

$$n_t + gn_x + \mu n = F(x,t), \tag{2.2.1}$$

with the right hand side defined as

$$F(x,t) = \alpha bn(l^-,t)\delta(x - l/\alpha) - bn(l^-,t)\delta(x - l), \tag{2.2.2}$$

for $\alpha > 1$ and $b > 0$. Observe that $F(x,t) \equiv 0$ when $x \neq l/\alpha$ or $x \neq l$, and we can straightforwardly find the solution of the resultant homogeneous equation for x in any of the three regions $R_1 = (0, l/\alpha)$, $R_2 = (l/\alpha, l)$, $R_3 = (l, \infty)$, as

$$n_i(x,t) = F_i(x - gt)e^{-\mu t}, \qquad i \in \{1, 2, 3\}, \tag{2.2.3}$$

where n_i denotes the solution of n within the region R_i and $F_i : \mathbb{R} \to \mathbb{R}$ are functions which we find below. This solution follows from the variable substitutions performed in (2.2.5) and the fact that the δ distributions are zero in each region.

Now consider the region R_1; in this region, from (2.1.3) we have

$$F_1(x) = n_0(x), \qquad 0 < x < \frac{l}{\alpha},$$

and from (2.1.2) we see that

$$F_1(-gt) = 0, \qquad 0 < t.$$

Therefore, we have

$$F_1(z) = n_0(z)H(z),$$

where H denotes the Heaviside function, so that

$$n_1(x,t) = \begin{cases} n_0(x-gt)e^{-\mu t} & 0 < t < \frac{x}{g}, \\ 0 & t > \frac{x}{g}. \end{cases} \tag{2.2.4}$$

In the following we assume that $n_0 \in L^1[0,\infty)$and that n_0 has finite isolated discontinuities, and we search for a solution $n(x,t)$ such that $n(\cdot,t) \in L^1[0,\infty)$ and is piecewise continuous for any $t \geq 0$. To proceed further we must consider the jump conditions across the boundaries of the regions R_i, $i \in \{1,2,3\}$. To do this we first find a functional equation for n.

2.2.1 Algebraic functional equation

In this section we derive a functional equation for $n(x,t)$. To this end first make the following substitutions in (2.1.5):

$$\xi = x - gt, \tag{2.2.5}$$

$$U(\xi,t) = U(x-gt,t) = n(x,t),$$

to yield the differential equation

$$D_2U(\xi,t) + \mu U(\xi,t) = \overline{F}(\xi,t) = F(\xi+gt,t),$$

where D_2 denotes the partial derivative operator with respect to the second argument. By use of an integrating factor the following expression is derived for U:

$$\begin{aligned} U(\xi,t) \;=\; & \frac{\alpha b}{g} H\left(t - \left[\frac{l}{g\alpha} - \frac{\xi}{g}\right]\right) n\left(l^-, \frac{l}{g\alpha} - \frac{\xi}{g}\right) e^{\mu\left[\frac{l}{g\alpha} - \frac{\xi}{g} - t\right]} \\ & - \frac{b}{g}\mathrm{H}\left(t - \left[\frac{l}{g} - \frac{\xi}{g}\right]\right) n\left(l^-, \frac{l}{g} - \frac{\xi}{g}\right) e^{\mu\left[\frac{l}{g} - \frac{\xi}{g} - t\right]} + C(\xi)e^{-\mu t}, \end{aligned}$$

where C is an arbitrary function of ξ yet to be determined. The substitution $n(x,t) = U(x-gt,t)$ is now used to give

$$\begin{aligned} n(x,t) &= \frac{\alpha b}{g}\mathrm{H}(x-l/\alpha)n\left(l^-, \frac{l}{g\alpha} - \frac{x}{g} + t\right) e^{\mu\left[\frac{l}{g\alpha}-\frac{x}{g}\right]} \\ &\quad -\frac{b}{g}\mathrm{H}(x-l)n\left(l^-, \frac{l}{g} - \frac{x}{g} + t\right) e^{\mu\left[\frac{l}{g}-\frac{x}{g}\right]} + C(x-gt)e^{-\mu t}. \end{aligned} \tag{2.2.6}$$

Using the fact that $n(x,0) = n_0(x)$, and $n(0,t) = 0$ for $t > 0$, we find

$$\begin{aligned} C(x) &= n_0(x)\mathrm{H}(x) - \frac{\alpha b}{g}\mathrm{H}(x-l/\alpha)n\left(l^-, \frac{l}{g\alpha} - \frac{x}{g}\right) e^{\mu\left[\frac{l}{g\alpha}-\frac{x}{g}\right]} \\ &\quad +\frac{b}{g}\mathrm{H}(x-l)n\left(l^-, \frac{l}{g} - \frac{x}{g}\right) e^{\mu\left[\frac{l}{g}-\frac{x}{g}\right]}, \end{aligned}$$

and on substituting the expression for $C(x)$ back into (2.2.7),

$$\begin{aligned} n(x,t) = n_0(x-gt)\mathrm{H}(x-gt)e^{-\mu t} + \frac{\alpha b}{g}n\left(l^-, \frac{l}{g\alpha} - \frac{x}{g} + t\right) e^{\mu\left[\frac{l}{g\alpha}-\frac{x}{g}\right]}\mathcal{H}_1(x,t) \\ -\frac{b}{g}n\left(l^-, \frac{l}{g} - \frac{x}{g} + t\right) e^{\mu\left[\frac{l}{g}-\frac{x}{g}\right]}\mathcal{H}_2(x,t). \end{aligned} \tag{2.2.7}$$

Here the functions $\mathcal{H}_1(x,t)$ and $\mathcal{H}_2(x,t)$ are defined as

$$\mathcal{H}_1(x,t) = \mathrm{H}\left(x - \frac{l}{\alpha}\right) - \mathrm{H}\left(x - \frac{l}{\alpha} - gt\right) = \begin{cases} 1 & \frac{l}{\alpha} < x < \frac{l}{\alpha} + gt, \\ 0 & \text{otherwise,} \end{cases},$$

$$\mathcal{H}_2(x,t) = \mathrm{H}(x-l) - \mathrm{H}(x-l-gt) = \begin{cases} 1 & l < x < l + gt, \\ 0 & \text{otherwise.} \end{cases}$$

We note that these two functions only take on the values 1 or 0 and the regions in which these functions take on these respective values is shown in Figure 2.1.

We observe equation (2.2.7) is a functional equation whose solution yields n. To solve this equation it is necessary to consider the jump conditions at $x = l/\alpha$ and $x = l$; a task to which we now turn.

2.2.2 Jump discontinuities in $n(x,t)$

In this section the jumps in $n(x,t)$ at $x = l/\alpha$ and $x = l$ are determined, and are used to find an expression for $F_3(l-gt)$ and a retarded functional equation for F_2.

For any $t > 0$, we have (from (2.2.7))

$$\begin{aligned} \lim_{x\to \frac{l}{\alpha}^-} n(x,t) &= n_0\left(\frac{l}{\alpha}^- - gt\right) H\left(\frac{l}{\alpha}^- - gt\right) e^{-\mu t} \\ \lim_{x\to \frac{l}{\alpha}^+} n(x,t) &= n_0\left(\frac{l}{\alpha}^+ - gt\right) H\left(\frac{l}{\alpha}^+ - gt\right) e^{-\mu t} + \frac{\alpha b}{g}n(l^-, t^-), \end{aligned}$$

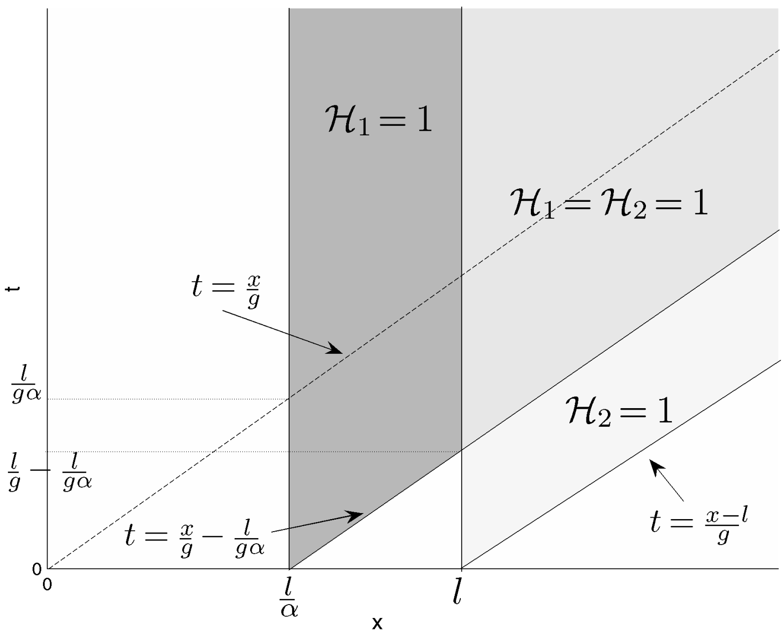


Figure 2.1: Regions of support for $\mathcal{H}_1$ and $\mathcal{H}_2$. $\mathcal{H}_1$ is non-zero for $\frac{l}{\alpha} < x < \frac{l}{\alpha} + gt$; $\mathcal{H}_2$ is non-zero for $l < x < l + gt$. The solution $n(x,t)$ is zero for $0 < x < \min\{gt, l/\alpha\}$.

where

$$n(l^-, t^-) = \lim_{\tau \to t^-} \lim_{x \to l^-} n(x, \tau).$$

Thus,

$$n\left(\frac{l}{\alpha}^+, t\right) - n\left(\frac{l}{\alpha}^-, t\right) = \frac{\alpha b}{g} n(l^-, t^-), \qquad \text{a.e. } t > 0. \tag{2.2.8}$$

Figure 2.1 shows that when $0 < t < \frac{l}{g} - \frac{l}{g\alpha}$, then $\mathcal{H}_1(l^+, t) = \mathcal{H}_1(l^-, t) = 0$. We therefore get

$$n(l^+, t) - n(l^-, t) = -\frac{b}{g} n(l^-, t^-), \qquad \text{a.e. } 0 < t < \frac{l}{g} - \frac{l}{g\alpha}. \tag{2.2.9}$$

Figure 2.1 also shows that when $t > \frac{l}{g} - \frac{l}{g\alpha}$, $\mathcal{H}_1(l^+, t) = \mathcal{H}_1(l^-, t) = 1$; so in this case we get

$$n(l^+, t) - n(l^-, t) = -\frac{b}{g} n(l^-, t^-) + \frac{\alpha b}{g}\left[n\left(l^-, \frac{l}{g\alpha} - \frac{l}{g} + t^-\right) - n\left(l^-, \frac{l}{g\alpha} - \frac{l}{g} + t^+\right)\right] e^{\mu\left[\frac{l}{g\alpha} - \frac{l}{g}\right]}, \tag{2.2.10}$$

where we note the possible discontinuity in the function n in time by utilising the symbols t^-, t^+ to denote t from below and above. We are now in a position to find an equation for the jump condition across the boundary of the regions R_2 and R_3. From Equations (2.2.9) and (2.2.10), we see that

$$F_3(l^+-gt)-F_2(l^--gt)=\begin{cases} -\frac{b}{g}F_2(l^--gt^-), & 0<t<\frac{l}{g}-\frac{l}{g\alpha}, \\ -\frac{b}{g}F_2(l^--gt^-)+\frac{\alpha b}{g}\left[F_2\left(2l^--\frac{l}{\alpha}-gt^-\right)\right. & \\ \qquad\qquad\left.-F_2\left(2l^--\frac{l}{\alpha}-gt^+\right)\right], & \frac{l}{g}-\frac{l}{g\alpha}<t, \end{cases} \tag{2.2.11}$$

where we use the convention that whenever two limits appear in the argument of a function, the limits are taken in the order they occur. For example $F_2(l^- - gt^-)$, denotes

$$\lim_{y\to gt^-}\lim_{x\to l^-}F_2(x-y).$$

Note that $F_2(l^- - gt^-)$ is equivalent to $F_2([l-gt]^+)$, when F_2 is piecewise continuous. Also, F_2 must be piecewise continuous in order to obtain a solution $n(x,t)$ which is piecewise continuous in x for all $t \geq 0$.

From Equation (2.2.11), we see that $F_3(l-gt)$ may be expressed solely in terms of F_2, with $F_3(x) = n_0(x)$ when $x > l$. All that remains now is to solve for F_2.

From equation (2.2.8), we find that the jump condition across the boundary of the regions R_1 and R_2 gives

$$F_2\left(\frac{l}{\alpha}^+-gt\right)-\lambda F_2(l^--gt^-) \;=\; n_0\left(\frac{l}{\alpha}-gt\right)\mathrm{H}\left(\frac{l}{\alpha}-gt\right), \qquad \text{a.e. } t>0,$$

where

$$\lambda=\frac{\alpha b}{g},$$

and we have used $F_1 = n_0(x)\mathrm{H}(x)$. It is convenient in the following to redefine the independent variable, and to facilitate this we let $z = \frac{l}{\alpha} - gt$, and $u = l - \frac{l}{\alpha} > 0$; it then follows that

$$F_2(z^+)=n_0(z)\mathrm{H}(z)+\lambda F_2((z+u)^+), \qquad z<\frac{l}{\alpha}, \tag{2.2.12}$$

For $\frac{l}{\alpha} < z < l$ we clearly have $F_2(z) = n_0(z)$, since $F_2(x) = n_0(x)$ when $\frac{l}{\alpha} < x < l$. It should be observed that (2.2.12) constitutes a retarded functional equation for F_2 when moving in the direction of the left-hand axis of z. Note that when we take $\delta(x-l)n(x,t) = \delta(x-l)n(l^+,t)$, as opposed to our original interpretation that $\delta(x-l)n(x,t) = \delta(x-l)n(l^-,t)$, we obtain a functional equation for F_2 of a similar form as we obtain here, but with $\lambda = \alpha b/(b+g)$.

We find a piecewise continuous solution for $F_2(z)$ in Section 2.2.3 below (for $\alpha = 2$; see Section 2.7 for general $\alpha > 1$). Thus, from (2.2.11) we see that, almost everywhere,

$$F_3(l-gt)=\left(1-\frac{b}{g}\right)F_2(l-gt), \quad t>0. \tag{2.2.13}$$

Equation (2.2.13) states the behaviour of $F_3(z)$ for $z < l$, where z is defined as the argument of F_3. For $z > l$ we merely need to note that $F_3(x) = n_3(x, 0)$ when $x > l$ (the domain of definition of $n_3(x,t)$ provides the restriction $x > l$). Thus, $F_3(z) = n_0(z)$ when $z > l$.

From (2.2.13), it can be seen that b/g is the proportion of cells dividing upon reaching size l. When $b \leq g$ this ratio can be interpreted as the probability of any given cell dividing when it reaches size l. Moreover, we require $b \leq g$ for the solution to have any physical relevance, since it is impossible to have a negative number of cells at any size. For, when n_0 is non-negative, we see that $F_1(z) = n_0(z)H(z)$ is non-negative for $z \leq l/\alpha$. Moreover, by (2.2.12) and the fact that $F_2(z) = n_0(z)$ for $l/\alpha < z < l$, we have $F_2(z)$ non-negative for $z \leq l$. Thus by (2.2.13) we require $b \leq g$ for the solution $n(x,t)$ to be non-negative.

We will now proceed to find a solution to $F_2(z)$ for the special case when $\alpha = 2$ (the general case is handled in Section 2.7).

2.2.3 Solution of the functional equation for $\alpha = 2$

We now solve the functional equation (2.2.12) for F_2 by recursion when $\alpha = 2$. Observe that the mathematics is simplified since when $\alpha = 2$, $u = l/\alpha = l/2$. It is possible to write down the solution for general α but the algebraic complexities make it cumbersome except for a specific α. We provide some considerations for more general α in the Section 2.7. In the $\alpha = 2$ case, (2.2.12) becomes

$$F_2(z) = \begin{cases} H(z)n_0(z), & \frac{l}{2} < z < l, \\ H(z)n_0(z) + \lambda F_2\left(\left[z + \frac{l}{2}\right]^+\right), & z < \frac{l}{2}. \end{cases}$$

From this we may conclude that, almost everywhere,

$$\begin{aligned} F_2(z) &= n_0(z) + \lambda n_0\left(z + \frac{l}{2}\right), && 0 < z < \frac{l}{2} \\ &= \lambda n_0\left(z + \frac{l}{2}\right) + \lambda^2 n_0(z + l), && -\frac{l}{2} < z < 0 \\ &= \lambda^2 n_0(z + l) + \lambda^3 n_0\left(z + \frac{3l}{2}\right), && -l < z < -\frac{l}{2}, \end{aligned}$$

and it follows by backward recursion that

$$F_2(z) = \lambda^m n_0\left(z + \frac{ml}{2}\right) + \lambda^{m+1} n_0\left(z + \frac{(m+1)l}{2}\right), \quad -\frac{ml}{2} < z < -\frac{(m-1)l}{2}, \tag{2.2.14}$$

where $0 \leq m \in \mathbb{Z}$. Note that $F_2(z)$ is continuous at $z = -ml/2$ only if

$$\begin{aligned} \lambda^m n_0(0^+) + \lambda^{m+1} n_0\left(\frac{l}{2}^+\right) &= \lambda^{m+1} n_0\left(\frac{l}{2}^-\right) + \lambda^{m+2} n_0(l^-) \\ \iff \qquad n_0(0) &= \lambda^2 n_0(l^-) - \lambda[n_0(x)]_{l/2^-}^{l/2^+}. \end{aligned}$$

Thus in most cases F_2, and therefore the solution $n(x,t)$, will be discontinuous.

We now have all the information we need to write the full analytical solution for $n(x,t)$ (in terms of the solution in the three regions) as:

$$n_1(x,t) = n_0(x-gt)e^{-\mu t}\mathrm{H}(x-gt), \quad t>0. \tag{2.2.15}$$

$$n_2(x,t) = \begin{cases} n_0(x-gt)e^{-\mu t}, & \frac{l}{2} < x-gt < l, \\ e^{-\mu t}\left[\lambda^m n_0\left(x-gt+\frac{ml}{2}\right) + \lambda^{m+1} n_0\left(x-gt+\frac{(m+1)l}{2}\right)\right], & \frac{-ml}{2} < x-gt < \frac{-(m-1)l}{2}, \\ & 0 \le m \in \mathbb{Z}, \end{cases} \tag{2.2.16}$$

$$n_3(x,t) = \begin{cases} n_0(x-gt)e^{-\mu t}, & l < x-gt, \\ \left(1-\frac{b}{g}\right) n_2(x,t), & x-gt < l, \end{cases} \tag{2.2.17}$$

where in (2.2.17), the domain of definition of n_2 in x has been extended to $l < x$.

We end this section with a small lemma:

Lemma 2.2.1. *When $n_0 \in L^1[0,\infty)$ is piecewise continuous, there exists a unique solution (up to a set of zero measure) $n(x,t)$ to* (2.2.1)*, with $n(x,\cdot) \in L^1[0,\infty)$ and piecewise continuous for every $t \ge 0$.*

Proof. Existence by the above construction, and uniqueness by standard contradiction: If u and v are two distinct solutions to (2.2.1) with the same initial condition then $(u-v)$ specifies a non-zero solution with initial condition identically zero. However, from the above working it can be seen that a zero initial condition will lead to the trivial solution. □

2.2.4 Periodic nature of $n(x,t)$ in time

In Section 2.7 we discuss the behaviour $F_2(z)$ for any $\alpha > 1$, and it is shown that $n(l^-,t)e^{Jt}$ is a temporally periodic function for some J when $t > \frac{l}{g\alpha}$, with a period $\frac{l(\alpha-1)}{g\alpha}$ when $t > \frac{l}{g\alpha}$. The value of J for general α is given in Equation (2.7.1) as

$$J = -\frac{g\alpha}{l(\alpha-1)} \ln\left(\frac{\alpha b}{g}\right) + \mu. \tag{2.2.18}$$

In the case $\alpha = 2$, we find that

$$J = -\frac{2g}{l} \ln\left(\frac{2b}{g}\right) + \mu. \tag{2.2.19}$$

Thus for $t > \frac{l}{g\alpha}$ we may express $n(l^-,t)$ as

$$n(l^-,t) = e^{-Jt}p(t), \tag{2.2.20}$$

where p is a periodic function of t with period $\frac{l(\alpha-1)}{g\alpha}$. In Section 2.7 it is shown that for $\alpha = 2$, we may express $p(t)$ as

$$p(t) = e^{(J-\mu)(t-j\frac{l}{2})}\left\{n_0\left(l - gt + j\frac{l}{2}\right)\right.$$
$$\left. +\lambda n_0\left(l - gt + (j+1)\frac{l}{2}\right)\right\}, \qquad (j+1)\frac{l}{2g} < t < (j+2)\frac{l}{2g},$$

for all $0 \leq j \in \mathbb{Z}$.

Considering general $\alpha > 1$ again, we see from (2.2.7) that for $t > x/g$ the solution $n(x,t)$ is periodic with exponential growth superimposed. Indeed, substituting $n(l^-, t) = e^{-Jt}p(t)$ into (2.2.7) gives

$$\begin{aligned} n(x,t) = {} & \frac{\alpha b}{g}p\left(\frac{l}{g\alpha} - \frac{x}{g} + t\right)e^{\mu\left[\frac{l}{g\alpha}-\frac{x}{g}\right]-Jt}H\left(x - \frac{l}{\alpha}\right) \\ & - \frac{b}{g}p\left(\frac{l}{g} - \frac{x}{g} + t\right)e^{\mu\left[\frac{l}{g}-\frac{x}{g}\right]-Jt}H(x-l), \end{aligned} \tag{2.2.21}$$

when $t > x/g$.

A clear example of periodic behaviour at a fixed x is given in Figure 2.4, where the solution is also observed to be growing exponentially in time.

2.2.5 Computational results

A computer program was written in MATLAB code to evaluate $n(x,t)$ for any initial conditions. Snapshots in time of an example solution $n(x,t)$ are shown in Figures 2.2 and 2.3. The parameter values $g = 0.3$ and $l = 3$ mean that the periodic function $h(t) - h(t - l/2g)$ has a period of five time-units. This periodic behaviour can be seen in Figure 2.3, with the same shape being repeated at multiples of five time-units. The snapshots at times that are 2.5 modulo 5 show a discontinuity in the solutions which travels to the right as time increases. When this discontinuity reaches $x = l$ it returns back to $x = l/2$ and in this way is kept in the solution indefinitely. A proportion $(1 - b/g)$ of the solution in R_2 leaks through l and propagates out to infinity.

Figure 2.4, showing the solution in time at $x = 2$, illustrates the periodic nature of the solution with exponential growth superimposed.

From the results up to this point it is seen that the solution to the transient cell growth problem has the following characteristics:

1. The solution exhibits an exponential growth or decay rate as determined by the value of J (given by Equation (2.2.19) for $\alpha = 2$ or (2.2.18) for general $\alpha > 1$).

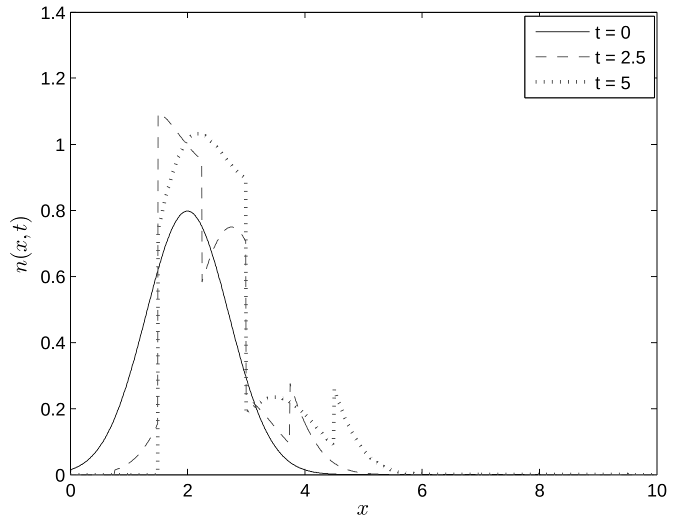


Figure 2.2: Snapshots showing the first five time-units behaviour of $n(x,t)$ with initial conditions given by a Gaussian distribution with mean 2 and standard deviation 0.5 truncated at $x = 0$. The parameter values for the model are $\alpha = 2$, $b = 0.2$, $g = 0.3$, $l = 3$ and $\mu = 0.025$.

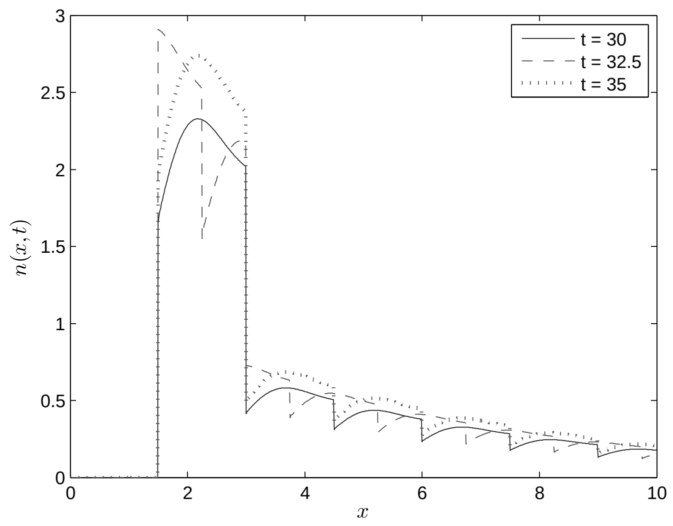


Figure 2.3: Snapshots showing the behaviour of $n(x,t)$ using the same parameters as in Figure 2.2 for time-units 30 to 35. By now we can see periodic behaviour (with period $\tau = 5$) in the section $1.5 < x < 3$, with the same shape being repeated at the times $t = 30$ and $t = 35$.

2. The solution exhibits periodic behaviour at each x for high enough t, with a temporal period

$$\frac{l(\alpha - 1)}{g\alpha}.$$

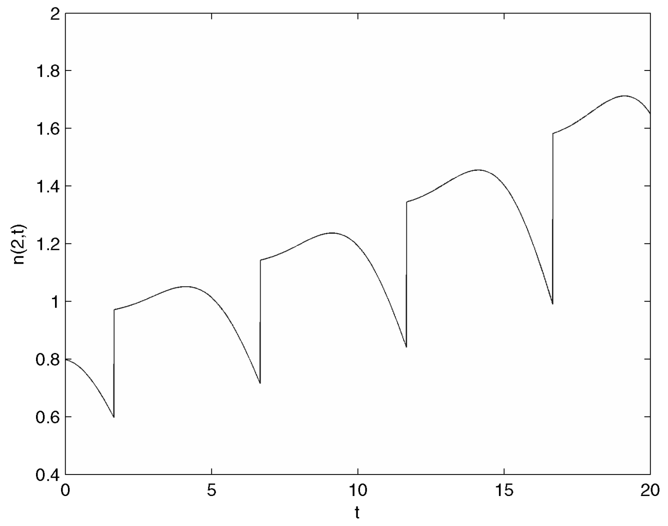


Figure 2.4: The behaviour of $n(x,t)$ (again using the same parameters as in Figure 2.2) at $x = 2$, illustrating the periodic nature of the solution superimposed with exponential growth.

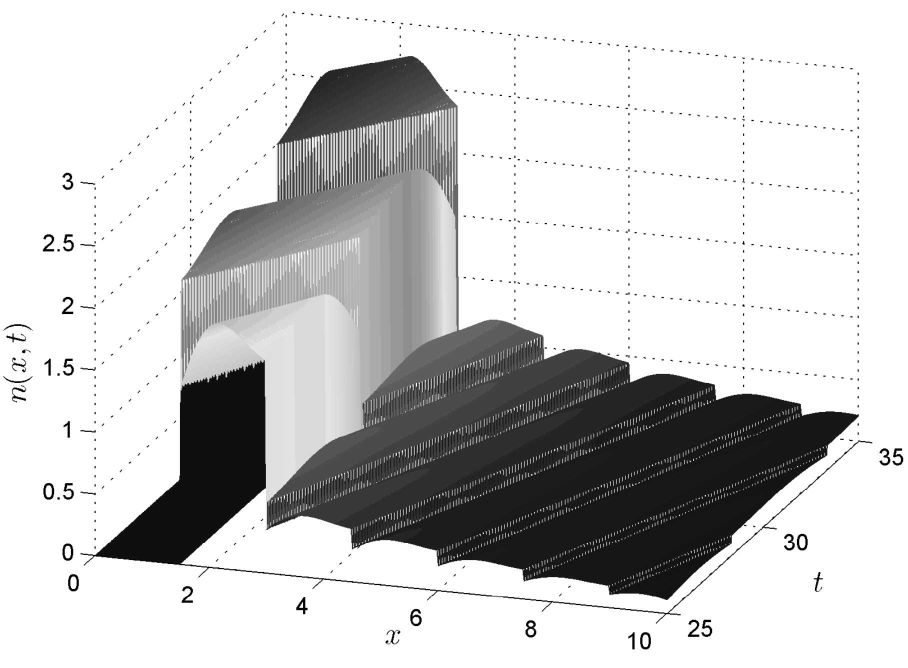


Figure 2.5: A full 3-dimensional plot of the behaviour of $n(x,t)$, using the same parameters as the previous three figures, showing a time window of length 2τ, where $\tau = 5$ is the period of the periodic part of the solution.

3. The solution depends continuously upon the initial value condition, n_0.

4. The solution does not in general exhibit any steady size-distribution behaviour.

This last point could lead one to believe that the model we have been studying, which has a hyperbolic principal symbol, is not appropriate for the phenomena (SSD behaviour) we are interested in. However, as we show in the next section a certain envelope of the solution which we have examined in this section has SSD type behaviour. Moreover, this envelope is identical in analytical detail to the separated solution obtained from the parabolic model (1.4.1) in I when $D \to 0$.

2.3 The relationship between the SSD solutions as $D \to 0$ and the solution when $D = 0$

In this section it is shown that the hull (defined below) of the solution $n(x,t)$ in the region $0 < x < gt$ is equivalent to an SSD solution to (2.2.1). The form of the SSD in this case is equivalent to the limit as $D \to 0$ of the SSDs when $D \neq 0$, as described in I. The SSDs in I was found by separation of variables and imposing the condition that y is a probability density function, giving the exponential growth rate $\Lambda = (\alpha - 1)by(l) - \mu$.

In the limit as $D \to 0$, the SSDs in I were shown to tend to the following form:

$$y(x) = \begin{cases} 0, & 0 < x < l/\alpha, \\ \frac{\alpha by(l)}{g} e^{-\frac{L}{g}(x - \frac{l}{\alpha})}, & l/\alpha < x < l, \\ \frac{by(l)}{g} e^{-\frac{L}{g}x} \left(\alpha e^{\frac{Ll}{g\alpha}} - e^{\frac{Ll}{g}} \right), & l < x, \end{cases} \tag{2.3.1}$$

where $L = \Lambda + \mu = (\alpha - 1)by(l)$. It shall be seen that the hull of the solution to $n(x,t)$ in the region $0 < x < gt$ is of a similar form.

2.3.1 Preliminary statements

We begin by defining a bounding envelope of the solutions found in the previous section; namely

$$N(x) = \sup_{t > x/g} n(x,t) e^{Jt}, \qquad x \geq 0, \tag{2.3.2}$$

where J (which may be positive or negative) is the decay rate of the solution, as defined for $\alpha = 2$ in (2.2.19) or for general α by (2.2.18). From the solution found in Section 2.2.3 it is apparent N is a bounded function of x only. We define the *hull* of the solution to (2.2.1) to be the probability-density distribution

$$H(x) = \frac{N(x)}{\int_0^\infty N(y)\ dy}, \qquad x \geq 0, \tag{2.3.3}$$

which produces an appropriate normalisation when the integral in the denominator is finite. Note that, by (2.2.14), for positive initial conditions the integral in (2.3.3) will always be non-zero and positive. The conditions for the integral in the denominator to be bounded are mentioned after Equation (2.3.7).

For any $\alpha > 1$ it is shown in the Section 2.7 that $n(l^-, t)$ behaves like a periodic function multiplied by an exponential growth/decay term for $t > \frac{l}{g\alpha}$. Thus, we may say

$$n(l^-, t) = e^{-Jt}p(t), \qquad t > \frac{l}{g\alpha}. \tag{2.3.4}$$

Moreover, we know that p is $\frac{l(\alpha-1)}{g\alpha}$-periodic.

Notice that we have taken the supremum in (2.3.2) over $t > x/g$. The reason for this is that $n(x, t)$ behaves periodically for any specific $x > 0$ when $t > x/g$. This can be seen by using (2.3.4) and (2.2.7) to express $n(x, t)$ when $t > x/g$.

Now, in the region $0 < x < gt$ (see Figure 2.1) we have $\frac{l}{g\alpha} - \frac{x}{g} + t > \frac{l}{g\alpha}$; or $t - \frac{x}{g} > 0$. So that

$$n\left(l^-, \frac{l}{g\alpha} - \frac{x}{g} + t\right) = e^{-Jt}p\left(\frac{l}{g\alpha} - \frac{x}{g} + t\right),$$

and by the fact that $\frac{l}{g} > \frac{l}{g\alpha}$ we also have

$$n\left(l^-, \frac{l}{g} - \frac{x}{g} + t\right) = e^{-Jt}p\left(\frac{l}{g} - \frac{x}{g} + t\right), \qquad 0 < x < gt.$$

We may thus substitute the right-hand sides of the above equations into (2.2.7) to give

$$\begin{aligned} n(x, t) = &\frac{\alpha b}{g} e^{-Jt} p\left(\frac{l}{g\alpha} - \frac{x}{g} + t\right) e^{\mu\left[\frac{l}{g\alpha} - \frac{x}{g}\right]} \mathcal{H}_1(x, t) \\ &- \frac{b}{g} e^{-Jt} p\left(\frac{l}{g} - \frac{x}{g} + t\right) e^{\mu\left[\frac{l}{g} - \frac{x}{g}\right]} \mathcal{H}_2(x, t), \end{aligned} \tag{2.3.5}$$

when $0 < x < gt$.

2.3.2 Calculation of the shape of the hull

In this section we calculate the shape of the hull of the transient solution. To expedite this we find $N(x)$ (which we also refer to as the hull) with the intent of scaling afterwards to finally obtain $H(x)$. Note that the shape of the hull is the similar when $\delta(x - l)n(x, t) = \delta(x - l)n(l^+, t)$ is chosen rather than $\delta(x - l)n(x, t) = \delta(x - l)n(l^-, t)$ (see Section 2.4 for more details).

To calculate the shape of the hull we first recognise that when $0 < x < gt$ we have $\mathcal{H}_1(x,t) = 1$ for all $x > l/\alpha$ and 0 otherwise; likewise $\mathcal{H}_2(x,t) = 1$ for all $x > l$ and 0 otherwise. Again we consider the three regions R_1, R_2 and R_3, defined at the beginning of Section 2.2.

When $x \in R_1$ and $x < gt$, equation (2.2.7) shows that $n(x,t) = 0$. Therefore, the hull in the region R_1 is

$$N(x) = 0.$$

When $x \in R_2$ and $x < gt$, we have

$$\begin{aligned} n(x,t) &= \frac{\alpha b}{g} n\left(l^-, \frac{l}{g\alpha} - \frac{x}{g} + t\right) e^{\mu\left[\frac{l}{g\alpha} - \frac{x}{g}\right]} \\ &= \frac{\alpha b}{g} e^{(J-\mu)\left[\frac{x}{g} - \frac{l}{g\alpha}\right]} e^{-Jt} p\left(\frac{l}{g\alpha} - \frac{x}{g} + t\right). \end{aligned}$$

Thus,

$$N(x) = \sup_{t > \frac{x}{g}} n(x,t) e^{Jt} = \frac{\alpha b}{g} e^{(J-\mu)\left[\frac{x}{g} - \frac{l}{g\alpha}\right]} \left\{ \sup_{t > \frac{l}{g\alpha}} p(t) \right\}.$$

The bracketed term in the above equation shall now be denoted by $N(l)$ since, given J as in (2.2.18), we see that

$$N(l^-) = \sup_{t > \frac{l}{g}} n(l^-, t) e^{Jt} = \sup_{t > \frac{l}{g}} p(t) = \sup_{t > \frac{l}{g\alpha}} p(t),$$

for any $x > 0$. This makes the hull continuous from the left (although we could just as easily let the hull be undefined at $x = l$).

Finally, when $x \in R_3$ and $x < gt$ we have

$$\begin{aligned} n(x,t) &= \frac{\alpha b}{g} n\left(l^-, \frac{l}{g\alpha} - \frac{x}{g} + t\right) e^{\mu\left[\frac{l}{g\alpha} - \frac{x}{g}\right]} \\ &\quad - \frac{b}{g} n\left(l^-, \frac{l}{g} - \frac{x}{g} + t\right) e^{\mu\left[\frac{l}{g\alpha} - \frac{x}{g}\right]} \\ \\ &= \frac{\alpha b}{g} e^{(J-\mu)\left[\frac{x}{g} - \frac{l}{g\alpha}\right]} e^{-Jt} p\left(\frac{l}{g\alpha} - \frac{x}{g} + t\right) \\ &\quad - \frac{b}{g} e^{(J-\mu)\left[\frac{x}{g} - \frac{l}{g}\right]} e^{-Jt} p\left(\frac{l}{g} - \frac{x}{g} + t\right). \end{aligned}$$

We observe that since p is $\left(\frac{l}{g} - \frac{l}{g\alpha}\right)$-periodic,

$$\begin{aligned} p\left(\frac{l}{g\alpha} - \frac{x}{g} + t\right) &= p\left(\frac{l}{g\alpha} - \frac{x}{g} + t + \frac{l}{g} - \frac{l}{g\alpha}\right) \\ &= p\left(\frac{l}{g} - \frac{x}{g} + t\right), \end{aligned}$$

so that when $l < x$,

$$\begin{aligned} N(x) &= \sup_{t > \frac{x}{g}} n(x,t)e^{Jt} \\ &= \frac{b}{g} e^{(J-\mu)\left[\frac{x}{g} - \frac{l}{g}\right]} \left(\alpha e^{(J-\mu)\left[\frac{l}{g} - \frac{l}{g\alpha}\right]} - 1 \right) N(l). \end{aligned}$$

We discuss the normalisation of N below.

2.3.3 Equivalence of the hull to the limiting SSD solutions as $D \to 0$

In I the SSD solutions in the limiting case are derived by separation of variables when $D \neq 0$ and then taking the limit as $D \to 0$. As was shown in Equation (2.1.8), when the condition that $y(x)$ is a probability density function is imposed, a relationship between $y(l)$ and the growth/decay rate Λ is given by $\Lambda = (\alpha - 1)by(l) - \mu$, where $y(l)$ is the value of the SSD at $x = l$. The limiting SSDs are then of the form given in Equation (2.3.1). These limiting SSDs are equivalent to the separated solution found by letting $D = 0$ at the outset (with a suitable change to the terms involving δ such as we made in (2.1.5)), and therefore, the limiting SSD from I, continuous from the left, is an SSD of (2.1.5).

Let us redefine the L used in (2.3.1) to L_1, so that $L_1 = \Lambda + \mu = (\alpha - 1)by(l)$. It should be noted that L_1 is the growth/decay rate Λ plus μ. Thus, if for the case of the hull we define

$$L = -J + \mu = \frac{g\alpha}{l(\alpha - 1)} \ln\left(\frac{\alpha b}{g}\right) \tag{2.3.6}$$

and recognise that $H(l)$ and $N(l)$ in this case are the analogues of $y(l)$ in I, we get

$$N(x) = \begin{cases} 0, & 0 < x < \frac{l}{\alpha}, \\ \frac{\alpha b N(l)}{g} e^{-\frac{L}{g}\left(x - \frac{l}{\alpha}\right)}, & \frac{l}{\alpha} < x < l \\ \frac{bN(l)}{g} e^{-\frac{L}{g}x}\left(\alpha e^{\frac{Ll}{g\alpha}} - e^{\frac{Ll}{g}}\right), & l < x. \end{cases} \tag{2.3.7}$$

with H given by (2.3.3). We see in Section 2.5.4 that the expression for $N(x)$ when $x > l$ is equal to $(1 - b/g)$ times the expression for $N(x)$ when $l/\alpha < x < l$. Thus there will be no appropriate normalisation H if and only if $L \leq 0$ and $b \neq g$, since then the integral from 0 to ∞ of $N(x)$ will be infinite. From the (2.3.6) we see that $L \leq 0$ if and only if $\alpha b \leq g$. Thus a necessary and sufficient condition for a normalisation of the hull to exist is $g < \alpha b$ or $b = g$; but $b = g$ implies $g < \alpha b$. Hence we find that a necessary and sufficient condition for a normalisation to exist is $g < \alpha b$.

Equation (2.3.7) is of exactly the same form as the limiting SSD solutions as $D \to 0$ with the understanding that $H(l)$ corresponds to $y(l)$ (see Equation 2.3.1 for a comparison). The only difference between them being the constants L and L_1. In both cases, however, L (or L_1) is the overall exponential growth rate of the solution plus μ.

The requirement that $L = L_1$ gives a restriction on $y(l)$ as follows:

$$(\alpha - 1)by(l) = \frac{\alpha g}{l(\alpha - 1)} \ln\left(\frac{\alpha b}{g}\right)$$

or

$$y(l) = \frac{\alpha g}{bl(\alpha - 1)^2} \ln\left(\frac{\alpha b}{g}\right). \tag{2.3.8}$$

Setting $y(l)$ to the above value and substituting this into Equation (2.3.1) (which gives the limiting SSD from I) makes the expression continuous from the left. Moreover, the hull when $D = 0$ is exactly equal to the limiting SSD as $D \to 0$ when $L = L_1$, $H(l) = y(l)$. Thus, the hull is the equivalent of the limiting SSD as $D \to 0$ with the requirement of continuity from the left. This SSD is a probability density function, so that we have appropriately normalised the hull by setting $H(l) = y(l)$. Note that such a limiting SSD only exists for $g < \alpha b$ (*i.e.* $\ln(\alpha b/g) > 0$, the same condition required for an appropriate normalisation of the hull to exist). Moreover, from Section 2.5.4 we see that the hull in the region $x > l$ is equal to $(1 - b/g)\phi(x)$, where $\phi(x)$ is the form of the hull in the region $l/\alpha < x < l$ with its domain of definition extended to $l < x$. The non-negativity of the hull therefore requires that $b \leq g$. Also, left-continuous limiting SSDs from I are only non-negative everywhere when $b \leq g$. Therefore, whenever a normalised, non-negative hull exists, there exists a corresponding left-continuous limiting SSD from I, and vice-versa. We noted above that the left-continuous limiting SSD is an SSD of (2.1.5). This implies that any normalised hull is also an SSD of (2.1.5).

We now make the following observations:

1. $H(x)$ is independent of the initial condition $n_0(x)$

2. $N(x)$ is a global attractor in the sense that for any finite interval $0 \leq x \leq a$,

$$\sup_{t \leq \tau < t + \frac{l(\alpha-1)}{g\alpha}} n(x,\tau)e^{J\tau} \to N(x),$$

   as $t \to \infty$. We henceforth refer to the above expression (with or without the scaling constant) as the *transient hull* of $n(x,t)$. The above convergence is seen from the fact that (by Equation (2.3.5)) $n(x,t)e^{Jt}$ is periodic with period $\frac{l(\alpha-1)}{g\alpha}$ when $t > x/g$. Therefore when $t > x/g$,

$$\sup_{t \leq \tau < t + \frac{l(\alpha-1)}{g\alpha}} n(x,\tau)e^{J\tau} = \sup_{t \geq x/g} n(x,t)e^{Jt} = N(x).$$

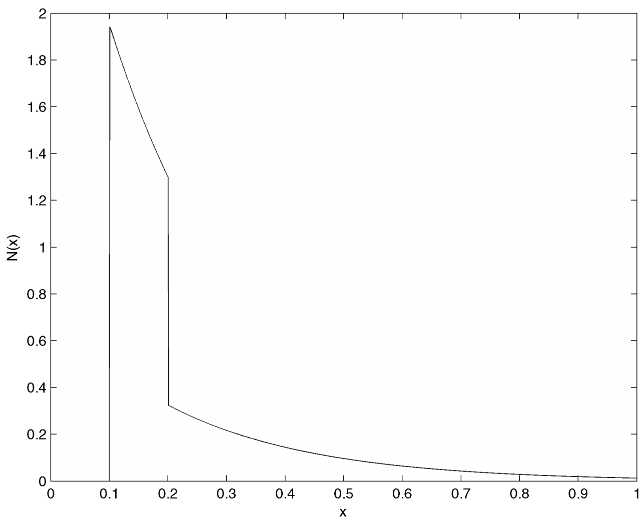


Figure 2.6: A plot of the hull when $\alpha = 2$, $l = 0.2$, $b = 3$, $g = 4$ and $N(l) = 1.3$.

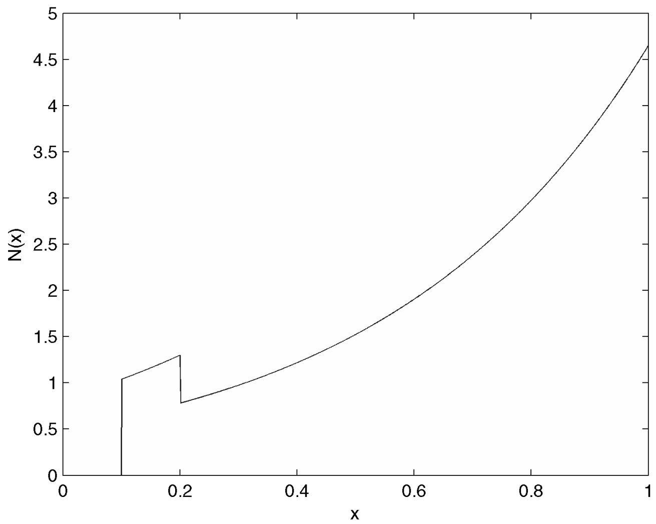


Figure 2.7: An unscaled hull when $\alpha b < g$. Parameters are $\alpha = 2$, $b = 2$, $g = 5$, $l = 0.2$, $N(l) = 1.3$. In this case there is no limiting SSD from I continuous from the left corresponding to the hull. Obviously in this case there is no appropriate normalisation to make the hull a probability density function.

3. If $g \geq \alpha b$ then $L \leq 0$ and $N \notin L^1$. This makes it impossible to match any limiting SSDs from I since in I they are probability density functions.

Figures 2.6 and 2.7 show examples of hulls for different sets of parameters. Figure 2.7 illustrates what the (unscaled) hull looks like when $g > \alpha b$; observe that it cannot be made into probability density function by scaling and hence cannot match any limiting SSD from I.

Finally, we note that when $\delta(x-l)n(x,t) = \delta(x-l)n(l^+,t)$ is chosen, we obtain $y(l) = \frac{\alpha g}{bl(\alpha-1)^2} \ln\left(\frac{\alpha b}{b+g}\right)$ when $L = L_1$. This is the condition for the limiting SSD to be continuous from the right. Similar comments for the right-continuous case apply as in the left-continuous case. Moreover, if we do not consider by convention that $n(x,t)$ is continuous from the left in x, the result regarding the equivalence of the hull and the limiting SSD continuous from the left holds for *almost every* $x > 0$ rather than for all x.

2.4 Every left-continuous limiting SSD from I has a right-continuous counterpart and vice-versa

In Section 2.1 we stated that identifying $\delta(x-l)n(x,t)$ with $\delta(x-l)n(l^-,t)$ was more physically realistic than the case where $\delta(x-l)n(x,t) = \delta(x-l)n(l^+,t)$. Here we compare the results of the two cases.

We already know from the above considerations that when we consider $\delta(x-l)n(x,t) = \delta(x-l)n(l^-,t)$, the transient hull of the solution tends to a limiting SSD from I, continuous from the left, when $g < \alpha b$. A similar result holds for the case when $\delta(x-l)n(x,t) = \delta(x-l)n(l^+,t)$, except in that case the transient hull of the solution tends to a limiting SSD from I, continuous from the right, when $\alpha b > b + g$. This is discussed more in Section 2.4.1.

Now, given a left-continuous limiting SSD with $\alpha b > g$, We desire to find b_0 such that the right-continuous limiting SSD with division constant b_0 will match the left-continuous SSD with division constant b. Let y_r denote the right-continuous limiting SSD and y_l denote the left-continuous limiting SSD. These limiting SSDs solve

$$gy' - \alpha\delta(x - l/\alpha)y(l) + b\delta(x-l)y(l) + \mu y(x) + \Lambda y(x) = 0,$$

for some $\Lambda \in \mathbb{R}$, where, in the case of y_l, we have $y_l(l) = y_l(l^-)$ and in the case of y_r we have $y_r(l) = y_r(l^+)$. The function $y_l(x)$ is a solution of (2.1.5) of the form $n(x,t) = e^{\Lambda t}y(x)$ which satisfies the boundary condition $n(0,t) = 0$, $t > 0$.

In the following we will use Equations (3.5) and (3.6) from I. These are the expressions for the second and third parts of the limiting SSD $y(x)$ expressed in Equation (2.3.1). We restate them below for convenience in Equations (2.4.1) and (2.4.2):

$$y(x) = \frac{\alpha b}{g} y(l) e^{-\frac{L}{g}\left(x - \frac{l}{\alpha}\right)}, \qquad l/\alpha < x < l, \tag{2.4.1}$$

$$= \frac{b}{g} y(l) e^{-\frac{L}{g}x} \left(\alpha e^{\frac{Ll}{g\alpha}} - e^{\frac{Ll}{g}}\right), \qquad x > l, \tag{2.4.2}$$

and we always have $y(x) = 0$ when $x < l/\alpha$; in the above equations $L = \Lambda + \mu$. From Equation (2.4.1) we then have

$$y_r\left(\frac{l}{\alpha}^+\right) = \frac{\alpha b_0}{g} y_r(l^+); \qquad y_l\left(\frac{l}{\alpha}^+\right) = \frac{\alpha b}{g} y_l(l^-).$$

In I it is shown that $\Lambda = b(\alpha - 1)y(l) - \mu$ when y is a probability density function. However, for the same value of Λ, any constant multiple of y will be an SSD if y is an SSD. Therefore, rather than regard Λ (and $L = \Lambda + \mu$) as a function of $y(l)$, as in I, we shall instead now regard this restriction as a necessary condition for y to be a probability density function (it is also sufficient).

In fact, the value of Λ is found by the equivalence of $y_l(x)$ with a hull of the form (2.3.7). This equivalence means that we must have

$$L = \frac{\alpha g}{l(\alpha - 1)} \ln\left(\frac{\alpha b}{g}\right),$$

and therefore, $\Lambda = L - \mu$ is given as,

$$\Lambda = \frac{\alpha g}{l(\alpha - 1)} \ln\left(\frac{\alpha b}{g}\right) - \mu. \tag{2.4.3}$$

We will now find left and right-continuous limiting SSDs which (may not be probability density functions) for a certain value of Λ and then verify that the SSDs are equivalent.

From Equations (2.4.1) and (2.4.2). we find that in both the left and right-continuous cases

$$y(l^-) = \frac{\alpha\{b \text{ or } b_0\}}{g} y(l) e^{-\frac{L}{g}\left(l - \frac{l}{\alpha}\right)}$$

$$y(l^+) = \frac{\alpha\{b \text{ or } b_0\}}{g} y(l) e^{-\frac{L}{g}\left(l - \frac{l}{\alpha}\right)} - \frac{\{b \text{ or } b_0\}}{g} y(l).$$

In the left-continuous case we have $y(l^-) = y(l)$, which implies, using the above identities, that

$$\frac{\alpha b}{g} e^{-\frac{L}{g}\left(l - \frac{l}{\alpha}\right)} = 1; \qquad y_l(l^+) = y_l(l^-) - \frac{b}{g} y_l(l^-) = \frac{g - b}{g} y_l(l^-). \tag{2.4.4}$$

The first equation is satisfied due to the fact that Λ is given by (2.4.3) and $L = \Lambda + \mu$. In the right-continuous case we obtain

$$\frac{\alpha b_0}{g} e^{-\frac{L}{g}\left(l - \frac{l}{\alpha}\right)} - \frac{b_0}{g} = 1; \qquad y_r(l^-) = y_r(l^+) + \frac{b_0}{g} y_r(l^+) = \frac{b_0 + g}{g} y_r(l^+).$$

The first of the above equations, combined with the first equation in (2.4.4), gives the requirement that

$$b_0 = \frac{bg}{g-b}. \tag{2.4.5}$$

If we now make the ratios $y_r(l^+)/y_r(l^-)$ and $y_l(l^+)/y_l(l^-)$ equal, we will have functions of the same shape, and it will remain only to choose $y_r(l^+)$ and $y_l(l^-)$ so that the functions are equal. Assuming that the above ratios are equal, then we must choose $y_r(l^+)$ and $y_l(l^-)$ such that

$$\frac{y_r(l^+)}{y_l(l^-)} = \frac{b_0}{b},$$

since then y_l and y_r will attain the same value as $x \to l/\alpha^+$ (according to Equation (2.4.1)), and will then be equal almost everywhere. We can then scale $y_r(l^+)$ and $y_l(l^-)$ such that y_r and y_l are probability density functions.

The condition that the ratios $y_r(l^+)/y_r(l^-)$ and $y_l(l^+)/y_l(l^-)$ are equal is equivalent to the condition that

$$\frac{g}{b_0+g} = \frac{g-b}{g}.$$

Multiplying both sides by $g(b_0+g)$ and expanding the product on the right-hand-side gives

$$g^2 = -b_0 b + b_0 g - bg + g^2.$$

This gives rise to the following relationship between b and b_0:

$$b_0 = \frac{bg}{g-b}; \qquad b = \frac{b_0 g}{b_0+g}. \tag{2.4.6}$$

(The first of the above equations was already obtained in (2.4.5)) If $b = g$ for the left-continuous limiting SSD $y_l(x)$, then there is no b_0 which produces a right-continuous counterpart $y_r(x)$. However, in this case the limiting shapes of $y_l(x)$ and the corresponding function $y_r(x)$ are equivalent as $b \to g$ (see Equation (2.3.7) for the shape of $y_l(x)$ and let $b \to g$). We can produce a similar analysis to the above by assuming the existence of a right-continuous limiting SSD $y_r(x)$ with division constant b_0 and attempting to find an equivalent left-continuous limiting SSD $y_l(x)$ with division constant b

2.4.1 Interpretation of b and b_0

From the above we see that $b_0 \to \infty$ as $b \to g$ and vice-versa. In the bulk of this chapter we have interpreted $\delta(x-l)n(x,t)$ as being equivalent to $\delta(x-l)n(l^-,t)$. In this case we saw that the probability of an individual cell dividing upon reaching size $x = l$ was b/g. Correspondingly, interpreting $\delta(x-l)n(x,t)$ as being equivalent to $\delta(x-l)n(l^+,t)$ and reproducing a similar analysis will give an identical solution as before as long as the division constant b_0 is chosen according to (2.4.6). Given that under the first interpretation the probability of a cell dividing upon reaching size $x = l$ is b/g, we find that the probability of a cell dividing upon reaching size $x = l$ under the second interpretation is

$$\frac{b_0}{b_0 + g}.$$

Also, under the second interpretation we do not need any restriction on the magnitude of b_0 to keep the solution $n(x, t)$ non-negative.

We found that the hull $N(x)$ from (2.3.7) had a finite integral–and therefore was able to be normalised to a probability density function via a division by $||N||_{L^1(0,\infty)}$–if and only if $\alpha b > g$. This used the interpretation $\delta(x - l)n(x, t) = \delta(x - l)n(l^-, t)$. However, when we use the interpretation $\delta(x - l)n(x, t) = \delta(x - l)n(l^+, t)$, we can see by the equivalence of the solutions under each interpretation that a normalisation exists if and only if

$$g < \alpha \frac{b_0 g}{b_0 + g},$$

where b_0 is the division rate constant for the model under the second interpretation. Multiplying both sides of the equation by $b_0 + g$ and dividing by g gives the requirement

$$b_0 + g < \alpha b_0.$$

The above condition is equivalent to condition (2.11) in I, which is a sufficient condition for the existence of an SSD to the single-compartment model with dispersion.

This suggests that perhaps in the limit, the SSDs from I tend to a right-continuous limiting SSD, rather than left-continuous. Indeed, the convergence in I as $D \to 0$ to the limiting SSDs was found by fixing $y(l)$ and examining how the formal SSD solution varied (with $L = b(\alpha - 1)y(l)$) as $D \to 0$. However, this is not quite correct. If we wish to see how the SSDs vary as $D \to 0$ we must examine how the SSDs themselves change, rather than the formal solution with fixed $y(l)$. This means that L (and consequently $y(l)$) must also vary as D varies.

It must be established that $y(l)$ converges to some value for the SSDs to converge at all. After this, we see that the convergence in I as $D \to 0$ to limiting SSDs happens uniformly in (l, ∞), while this is not true of the convergence in $(l/\alpha, l)$. Thus, the limiting form of the SSDs as $D \to 0$ is continuous from the right.

So, when considering limits, it is probably better to take the right-continuous limiting SSD than the left. Still, when $D = 0$, it is reasonable to concentrate on the case where $\delta(x-l)n(x, t) = \delta(x - l)n(l^-, t)$, since that is the more biologically sound (cells of size greater than l do not take part in the cell-division process). Moreover, under the interpretation of b and b_0 above, as long as the probability of cell-division is the same in both cases, the limiting SSDs are the same, regardless of continuity from the left or right.

2.5 Variable growth rate and the shape of the hull

We now address the problem of having a variable growth rate in (2.1.5) depending on x, and what effect this has on the shape of the hull. For the remainder of this chapter we use the interpretation that $\delta(x-l)n(x,t) = \delta(x-l)n(l^-,t)$. (We shall see that the variable growth rate case reduces to the constant growth rate case under certain transformations so that a similar equivalence of solutions holds, under different interpretations of $\delta(x-l)n(x,t)$, to that mentioned in 2.4.1.)

Let $0 < g(x)$, $x \geq 0$, be a positive continuous function for the growth-rate of cells of size x instead of a constant g as we have used up to this point, then for constant $\mu \geq 0$ we obtain, from (2.1.5), the equation

$$n_t + g(x)n_x + g'(x)n + \mu n = \alpha b\delta(x - l/\alpha)n(l^-,t) - b\delta(x-l)n(l^-,t). \qquad (2.5.1)$$

The use of a variable g function can allow the one compartment model to represent different stages of cell-growth, in which different growth rates might be experienced. In [4, 5], the phases G_1 and G_2 of human cell growth, occurring immediately after (G_1) or before cell division (G_2), effectively act as (stochastic) time delays. This may be approximated loosely by a growth function which is constant except on two finite intervals around l/α and l where the growth rate is reduced.

Equation (2.5.1) can be reduced to a form similar to (2.2.1) by a series of transformations which shall now be shown. Let

$$x' = \int_0^x \frac{1}{g(s)}\,ds; \qquad u(x',t) = n(x,t). \qquad (2.5.2)$$

Then

$$g(x)n_x = g(x)u_{x'}\frac{\partial x'}{\partial x} = u_{x'}.$$

Now let $h(x') = g'(x)$. We then have

$$u_t + u_{x'} + h(x')u + \mu u = \alpha b\delta(x - l/\alpha)n(l^-,t) - b\delta(x-l)n(l^-,t). \qquad (2.5.3)$$

We now make note of the fact that

$$\begin{aligned}
\int \delta(x-l)n(l^-,t)\ dx' &= \int \frac{\delta(x-l)}{g(x)}n(l^-,t)\ dx \\
&= H(x-l)\frac{n(l^-,t)}{g(l)} \\
&= H(x'-x'(l))\frac{u(x'(l)^-,t)}{g(l)},
\end{aligned}$$

and also of the fact that a similar result holds when we replace l by l/α. Therefore if we integrate both sides of (2.5.3) with respect to x' and subsequently differentiate by x', we obtain

$$u_t + u_{x'} + h(x')u + \mu u = \frac{\alpha b}{g(l/\alpha)}\delta(x'-x'(l/\alpha))u(x'(l)^-,t) - \frac{b}{g(l)}\delta(x'-x'(l))u(x'(l)^-,t).$$

Finally, let

$$w(x',t) = u(x',t)\exp\left[\int_0^{x'} h(s)\ ds\right]. \tag{2.5.4}$$

Then

$$u_t = w_t \exp\left[-\int_0^{x'} h(s)\ ds\right]; \qquad u_{x'} = (w_{x'} - h(x')w)\exp\left[-\int_0^{x'} h(s)\ ds\right].$$

Thus, when we express (2.5.1) using the independent variable x' and dependent variable w, we obtain

$$\begin{aligned}
(w_t + w_{x'} + \mu w)\exp\left[-\int_0^{x'} h(s)\ ds\right] &= \frac{\alpha b}{g(l/\alpha)}\delta(x'-x'(l/\alpha))w(x'(l)^-,t)\exp\left[-\int_0^{x'(l)} h(s)\ ds\right] \\
&\quad -\frac{b}{g(l)}\delta(x'-x'(l))w(x'(l)^-,t)\exp\left[-\int_0^{x'(l)} h(s)\ ds\right],
\end{aligned}$$

implying

$$\begin{aligned}
w_t + w_{x'} + \mu w &= \frac{\alpha b}{g(l/\alpha)}\delta(x'-x'(l/\alpha))w(x'(l)^-,t)\exp\left[-\int_{x'(l/\alpha)}^{x'(l)} h(s)\ ds\right] \\
&\quad -\frac{b}{g(l)}\delta(x'-x'(l))w(x'(l)^-,t). \qquad (2.5.5)
\end{aligned}$$

Notice that the differential equation above is similar to (2.2.1) with $g = 1$. The differences being that the constants multiplying the delta functions have been changed.

2.5.1 The hull of w

In this section we find the hull of w, which we shall then use to find the hull of n for a general positive growth function $g(x)$. The hull in this case is derived from the solution in the region $x' < t$, since w has an effective constant growth-rate of $g = 1$ and the hull for constant growth rate is derived from the solutions in the region $x < gt$. In this case $x' < t$ is a sufficient condition for the onset of periodicity, in the same way that $x < gt$ was sufficient in the constant growth-rate case. First, notice that

$$\begin{aligned}\frac{\alpha b}{g(l/\alpha)} \exp\left[-\int_{x'(l/\alpha)}^{x'(l)} h(s)\ ds\right] &= \frac{\alpha b}{g(l/\alpha)} \exp\left(-\int_{l/\alpha}^{l} \frac{g'(\xi)}{g(\xi)}\ d\xi\right)\\ &= \frac{\alpha b}{g(l/\alpha)} \frac{g(l/\alpha)}{g(l)} = \frac{\alpha b}{g(l)}.\end{aligned}$$

This simplifies (2.5.5), so that it is now virtually the same as the constant growth case (2.2.1) when $g = 1$.

Similar steps to those used in the case where g is constant may now be taken to find the solution of w. As mentioned above, w satisfies a slightly modified Equation (2.2.1) for $g = 1$. Note that $x'(l/\alpha) < x'(l)$; therefore we can treat $x'(l)$ and $x'(l/\alpha)$ much like l and l/α in the case with constant g to give the result that $w(x'(l), t)$ is a $[x'(l) - x'(l/\alpha)]$-periodic function multiplied by an exponential function for $t > x'(l/\alpha)$. Specifically

$$w(x'(l), t) = e^{-Jt} p(t), \qquad t > x'(l/\alpha),$$

where $p(t)$ is the afore-mentioned periodic function and

$$J = -[x'(l) - x'(l/\alpha)]^{-1} \ln\left(\frac{\alpha b}{g(l)}\right) + \mu.$$

This leads to a hull of the same shape as in the constant growth case with $\frac{b}{g}$ replaced by $\frac{b}{g(l)}$ wherever it appears. The hull must then be multiplied by

$$\exp\left[-\int_0^{x'} h(s)\ ds\right]$$

to find the hull U of u. Following this, the hull N of n is

$$N(x) = U\left(\int_0^x \frac{1}{g(s)}\ ds\right).$$

From the above observations, we find the hull W of w to be

$$\begin{aligned}
W(x') &= 0, \qquad 0 < x' < x'\left(\frac{l}{\alpha}\right),\\
W(x') &= \frac{\alpha b}{g(l)} W(x'(l)) e^{-L\left(x' - x'\left(\frac{l}{\alpha}\right)\right)}, \qquad x'\left(\frac{l}{\alpha}\right) < x' < x'(l)\\
W(x') &= \frac{b}{g(l)} W(x'(l)) e^{-L(x' - x'(l))} \left(\alpha e^{-L\left(x'(l) - x'\left(\frac{l}{\alpha}\right)\right)} - 1\right)\\
&= \frac{b}{g(l)} W(x'(l)) e^{-Lx'} \left(\alpha e^{Lx'\left(\frac{l}{\alpha}\right)} - e^{Lx'(l)}\right), \qquad x'(l) < x'.
\end{aligned}$$

where $L = -J + \mu$ as in the constant growth case.

Remark: The hull W is an attractor of the transient hull,

$$\sup_{t \le \tau < t + x'(l) - x'(l/\alpha)} w(x', \tau) e^{J\tau}$$

in the same way as in the constant growth case (*i.e.* uniformly on finite intervals $[0, a]$, $0 < a < \infty$). Correspondingly we have

$$N(x) = \sup_{t > x'} \; w(x', t) \exp\left[\int_0^{x'} h(s)\; ds + Jt\right]$$

is an attractor of the transient hull of n, given by

$$\sup_{t \le \tau < t + x'(l) - x'(l/\alpha)} w(x', \tau) \exp\left[\int_0^{x'} h(s)\; ds + J\tau\right].$$

Thus, we see that the qualitative behaviour of $n(x, t)$ with positive variable growth rate is similar to that for constant growth rate. In the above statements all hulls have been left unscaled.

2.5.2 A consideration to simplify the calculation of the hull of n

We claim that the hull $N(x)$ of $n(x, t)$, for variable growth-rate $g(x)$, satisfies the differential equation:

$$(g(x)N(x))' + LN(x) = \alpha b\delta(x - l/\alpha)N(l^-) - b\delta(x - l)N(l^-). \tag{2.5.6}$$

Putting the above equation through the transforms described in Equations (2.5.2) and (2.5.4); having $N(x)$ transform to $U(x')$ via the transformation in (2.5.2), then to $W(x')$ via the transformation in (2.5.4), we find that (2.5.6) is satisfied if and only if

$$W' + LW = \frac{\alpha b}{g(l)}\delta(x' - x'(l/\alpha))W(x'(l)^-) - \frac{b}{g(l)}\delta(x' - x'(l))W(x'(l)^-). \tag{2.5.7}$$

It is easy to check that $W(x')$ satisfies Equation (2.5.7). Thus, after applying reverse transformations to W and U, we see that the hull $N(x)$ satisfies (2.5.6).

Note that (2.5.6) is the same as that for the separated solution (SSD) $y(x)$ in I with $D = 0$ (manipulate Equation (2.1.6) for y, using $L = \Lambda + \mu$ and $B(x) = b\delta(x - l)$). However, here we cannot say that the hull matches a limiting SSD as $D \to 0$, since the separated problem for variable g when $D \neq 0$ seems very difficult, so a proof is yet to be found.

2.5.3 The general shape of $N(x)$

The solution to $N(x)$ is obtained by using the fact that

$$g(x)N'(x) + (L + g'(x))N(x) = 0, \qquad x \notin \{l, l/\alpha\},$$

and jump conditions on N at $x = l/\alpha$ and $x = l$, found by integrating both sides of (2.5.6) over an interval containing l (resp. l/α) and letting both limits of the integral tend to l (resp. l/α). The jump conditions are as follows:

$$[N]_{l/\alpha^-}^{l/\alpha^+} = \frac{\alpha b}{g(l/\alpha)} N(l^-); \qquad [N]_{l^-}^{l^+} = -\frac{b}{g(l)} N(l^-).$$

From this we find a three-part solution:

$$N_i(x) = C_i \exp\left(-\int_0^x \frac{L}{g(s)}\, ds\right) [g(x)]^{-1}, \qquad i \in \{1, 2, 3\},$$

where the domain of N_i is R_i for $i \in \{1, 2, 3\}$ and R_i is as we have defined in Section 2.2. Note that we set $N(l) = N(l^-) = N_2(l)$.

The condition that $N_2(l) = N(l)$ fixes the value of C_2, giving

$$N_2(x) = N(l) \exp\left(\int_x^l \frac{L}{g(s)}\, ds\right) \frac{g(l)}{g(x)}.$$

The jump condition at $x = l$ fixes C_3 and leads to the result that $N_3(x) = (1 - b/g(l))N_2(x)$, where the domain of definition of $N_2(x)$ has been extended to $l < x$.

Finally, the jump condition at $x = \frac{l}{\alpha}$ implies

$$N_1(l/\alpha) = N_2(l/\alpha) - \frac{\alpha b}{g(l/\alpha)} N_2(l),$$

so that

$$\begin{aligned} C_1 &= \left[N_2(l/\alpha) - \frac{\alpha b}{g(l/\alpha)} N_2(l)\right] \exp\left(\int_0^{l/\alpha} \frac{L}{g(s)}\, ds\right) g(l/\alpha) \\ &= N_2(l) \left[\exp\left(\int_0^l \frac{L}{g(s)}\, ds\right) g(l) - \alpha b \exp\left(\int_0^{l/\alpha} \frac{L}{g(s)}\, ds\right)\right]. \end{aligned}$$

Therefore,

$$N_1(x) = \frac{N_2(l)}{g(x)} \exp\left(\int_x^{l/\alpha} \frac{L}{g(s)}\, ds\right) \left[\exp\left(\int_{l/\alpha}^l \frac{L}{g(s)}\, ds\right) g(l) - \alpha b\right]. \tag{2.5.8}$$

The choice of L, however, forces $N_1(x)$ to be identically zero, since $L = [x'(l) - x'(l/\alpha)]^{-1} \ln\left(\frac{\alpha b}{g(l)}\right)$, and so, in (2.5.8),

$$\exp\left(\int_{l/\alpha}^l \frac{L}{g(s)}\, ds\right) g(l) - \alpha b = \exp(L[x'(l) - x'(l/\alpha)])g(l) - \alpha b = \frac{\alpha b}{g(l)} g(l) - \alpha b = 0.$$

We may thus summarise the solution of the hull $N(x)$ as follows:

$$N(x) = \begin{cases} 0, & 0 < x < l/\alpha, \\ N(l) \exp\left(\int_x^l \frac{L}{g(s)}\, ds\right) \frac{g(l)}{g(x)}, & l/\alpha < x < l, \\ \left(1 - \frac{b}{g(l)}\right) N(l) \exp\left(\int_x^l \frac{L}{g(s)}\, ds\right) \frac{g(l)}{g(x)}, & l < x, \end{cases} \tag{2.5.9}$$

with N continuous from the left at l.

From this it can be seen that a necessary and sufficient condition for positivity of the hull is that $b \leq g(l)$. This is the analogue of the condition $b \leq g$ for positivity of the hull for constant growth rate. Moreover, for the unscaled hull to have a finite integral the condition we require is $g(l) < \alpha b$. Thus, the conditions needed for the hull to be a probability density function are $b \leq g(l) < \alpha b$.

2.5.4 Verification that the variable $g(x)$ hull reduces to the constant g hull when $g(x)$ is constant

We now show that the above expression matches (2.3.7) when g is constant. Let N_a denote the hull from (2.3.7) and N_b denote the hull from (2.5.9) when g is constant, and assume that $N_a(l) = N_b(l)$.

Consider (2.5.9) when g is constant. It is easy to check that L in this case is the same as in (2.3.7), namely

$$L = \frac{g\alpha}{l(\alpha-1)} \ln\left(\frac{\alpha b}{g}\right).$$

The hull $N_b(x)$, in the region $l/\alpha < x \leq l$, is now,

$$\begin{aligned} N_b(l)\exp\left[\frac{L}{g}(l-x)\right] &= N_b(l)\frac{\alpha b}{g}\exp\left\{\frac{L}{g}\left[l-x-\frac{g}{L}\ln\left(\frac{\alpha b}{g}\right)\right]\right\} \\ &= N_b(l)\frac{\alpha b}{g}\exp\left[-\frac{L}{g}\left(x-\frac{l}{\alpha}\right)\right], \end{aligned} \tag{2.5.10}$$

which is the same expression as in (2.3.7). Now consider (2.3.7) when $l < x$. Let $\phi(x) = N_a(x)$ for $l/\alpha < x \leq l$, and extend the domain of definition of ϕ to $l < x$. Note that in the region $l < x$ we have

$$N_a(x) = \phi(x) - \frac{b}{g}N_a(l)\exp\left[-\frac{L}{g}(x-l)\right].$$

But from what we saw in (2.5.10) we can now see that

$$N_a(l)\exp\left[-\frac{L}{g}(x-l)\right] = \phi(x).$$

Thus, Equations (2.3.7) and (2.5.9) agree for $l/\alpha < x$. Moreover ,both equations agree when $0 < x < l/\alpha$, where they both specify the hull as being zero. Thus, they specify the same hull when g is constant.

In the calculation of the hull for variable g the supremum of the periodic function $p(t)$ is taken over $t < x'$ (because the effective growth-rate of the transformed function w was $g = 1$; see Section 2.5.1), which becomes $t < x/g$, as expected, when g is constant.

2.5.5 Example of a specific growth function

We now give an example growth function $g(x)$ to illustrate the effect that the varying growth rate has on the shape of the hull. We have constructed $g(x)$ so that it is approximately constant except in two regions around l/α and l respectively. The specific function we use here is

$$g(x) = 3 - 2G\left(x, \frac{l}{\alpha}\right) - G(x, l),$$

where

$$G(x, y) = \exp\left(\frac{-(x-y)^2}{2(0.2)^2}\right).$$

A plot of this growth function is shown in Figure 2.8. The regions of slower growth in the above growth function are designed to simulate time-lag before and after cell division, as in the G_1 and G_2 phases of human cell growth mentioned above.

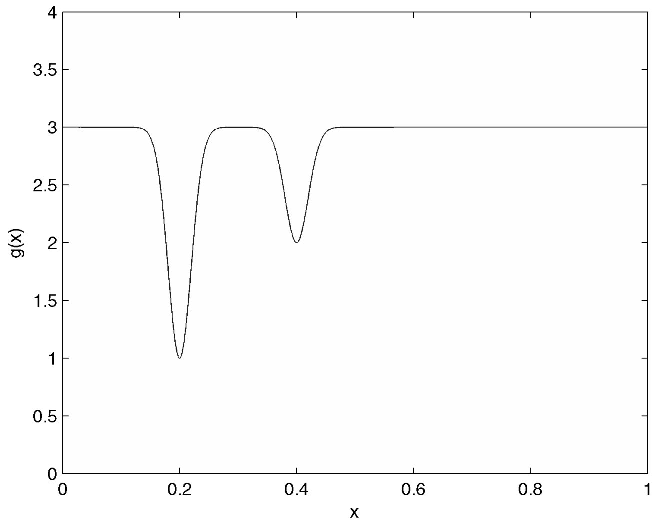


Figure 2.8: An example growth function $g(x)$. It consists of a constant minus two gaussian-like functions with peaks at $\frac{l}{\alpha}$ and l. In this case $l = 0.4$ and $\alpha = 2$. The regions of slower growth in the above growth function are designed to simulate time-lag before and after cell division. This is characteristic of human cell-growth, where the cells go through G_1-phase immediately after cell division and G_2-phase immediately prior.

The hull corresponding to the growth function $g(x)$ is shown in Figure 2.9. One would expect the cells to collect in the regions of slower growth, and thus affect the shape of the hull in a similar way, and this is what we see in the figure.

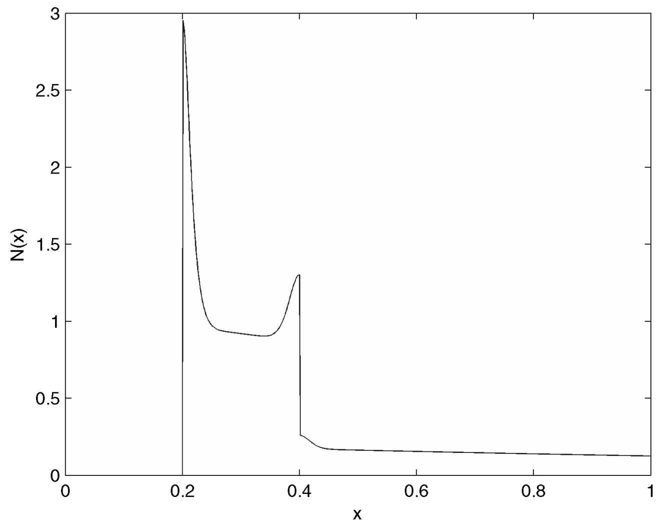


Figure 2.9: The hull corresponding to the growth function in Figure 2.8, with $\alpha = 2$, $b = 1.6$, $l = 0.4$ and $N(l) = 1.3$. The cells tend to collect in the regions of slower growth.

2.6 Conclusions

The transient hull of the solution to (2.2.1) with continuous $g(x) > 0$, $x \geq 0$, displays SSD behaviour when the growth and division parameters satisfy the inequality

$$b \leq g(l) < \alpha b.$$

It was found that $g(l) < \alpha b$ in order for the (unscaled) hull to be in L^1; this is essential in order for the hull H to be a probability density function as is also required in I for $y(x)$. The transient hull distributions track along the SSD path

$$n(x,t) \sim H(x) e^{\Lambda t},$$
$$\Lambda = -J$$

for large time t where the sign of the exponent J is determined by the equation (2.2.18). Therefore the cell cohort has survival or extinction outcomes if

$$\ln\left(\frac{\alpha b}{g(l)}\right)\left[\int_{l/\alpha}^{l} \frac{1}{g(s)}\, ds\right]^{-1} \begin{cases} > \mu & \text{survival } (J < 0), \\ < \mu & \text{extinction } (J > 0). \end{cases}$$

This applies to both of the constant-growth and variable-growth cases. In the constant-growth case these conditions become:

$$\ln\left(\frac{\alpha b}{g}\right)\frac{\alpha g}{l(\alpha-1)}\begin{cases} > \mu & \text{survival } (J<0), \\ < \mu & \text{extinction } (J>0). \end{cases}$$

When g is constant, the hull of the solution for the model (2.1.5) without dispersion provides a limiting form for the SSDs of I with dispersion as the dispersion tends to zero.

A variable growth-rate changes the shape of the hull, and if it can be shown that the hull in this case is the limit as $D \to 0$ of SSDs dependent on D, then potentially the general expression for the variable growth-rate hull could be used in the inverse problem of determining the growth rate at each size of a population of cells.

2.7 Periodic behaviour of $n(x,t)$ when t is great enough

2.7.1 Periodic behaviour of $n_2(l,t)$ as $t \to \infty$ for $1 < \alpha$

In this section it is shown that $n_2(l,t)$ is the product of a $\frac{l(\alpha-1)}{g\alpha}$-periodic function and an exponential function for $t > \frac{l}{g\alpha}$ when $1 < \alpha$; where

$$n_2(l,t) = F_2(l-gt)e^{-\mu t}$$

as in Equation (2.2.3).

For $l/\alpha < x < l$, we know that $F_2(x) = n_0(x)\mathrm{H}(x)$. This, combined with (2.2.12) gives us the necessary information to calculate the behaviour of $F_2(z)$ as z decreases. In the following working we will assume $n_0(z) = 0$ for $z \leq 0$. Thus, $n_0(z) = n_0(z)\mathrm{H}(z)$. First let $\lambda = \frac{\alpha b}{g}$, then from Equation (2.2.12) we have (almost everywhere)

$$F_2(z) = n_0(z)\mathrm{H}(z) + \lambda n_0\left(z + l - \frac{l}{\alpha}\right), \quad \frac{l}{\alpha} - \left(l - \frac{l}{\alpha}\right) < z < \frac{l}{\alpha}.$$

It is easily shown by recursion that

$$\begin{aligned} F_2(z) &= H(z)n_0(z) + \lambda n_0\left(z + l - \frac{l}{\alpha}\right)H\left(z + l - \frac{l}{\alpha}\right) + \ldots + \lambda^m n_0\left(z + m\left[l - \frac{l}{\alpha}\right]\right), \\ &\text{when} \qquad \frac{l}{\alpha} - m\left(l - \frac{l}{\alpha}\right) < z < \frac{l}{\alpha} - (m-1)\left(l - \frac{l}{\alpha}\right), \end{aligned}$$

for all $0 < m \in \mathbb{Z}$. Moreover, this shows that whenever n_0 is piecewise continuous we have $F_2(z)$ piecewise continuous. However, $H(z) = 0$ when $z < 0$ and it is desirable that terms equal to zero be removed from the expression for $F_2(z)$. To this end we proceed by noting that there exists some $0 \leq k \in \mathbb{Z}$ such that

$$\frac{l}{\alpha} - k\left(l - \frac{l}{\alpha}\right) \geq 0; \qquad \frac{l}{\alpha} - (k+1)\left(l - \frac{l}{\alpha}\right) < 0.$$

Thus, let $G(z) = F_2(z)$ in the region $\frac{l}{\alpha} - k\left(l - \frac{l}{\alpha}\right) < z < \frac{l}{\alpha} - (k-1)\left(l - \frac{l}{\alpha}\right)$. That is, let

$$\begin{aligned} G(z) &= n_0(z) + \ldots + \lambda^k n_0\left(z + k\left[l - \frac{l}{\alpha}\right]\right), \\ \text{when} \quad & \frac{l}{\alpha} - k\left(l - \frac{l}{\alpha}\right) < z < \frac{l}{\alpha} - (k-1)\left(l - \frac{l}{\alpha}\right). \end{aligned}$$

Since $\frac{l}{\alpha} - k\left(l - \frac{l}{\alpha}\right) > 0$, we know that $\frac{l}{\alpha} - (k-1)\left(l - \frac{l}{\alpha}\right) > \left(l - \frac{l}{\alpha}\right)$. Thus we have

$$F_2(z) = \begin{cases} G(z) & \frac{l}{\alpha} - k\left(l - \frac{l}{\alpha}\right) < z < \left(l - \frac{l}{\alpha}\right), \\ n_0(z) + \lambda G\left(z + l - \frac{l}{\alpha}\right) & 0 < z < \frac{l}{\alpha} - k\left(l - \frac{l}{\alpha}\right). \end{cases}$$

Again, it is easily shown by induction that

$$F_2(z) = \begin{cases} \lambda^j G\left(z + j\left[l - \frac{l}{\alpha}\right]\right) & \frac{l}{\alpha} - (k+j)\left(l - \frac{l}{\alpha}\right) < z < -(j-1)\left(l - \frac{l}{\alpha}\right), \\ \\ \lambda^j n_0\left(z + j\left[l - \frac{l}{\alpha}\right]\right) & \\ +\lambda^{j+1} G\left(z + (j+1)\left[l - \frac{l}{\alpha}\right]\right) & -j\left(l - \frac{l}{\alpha}\right) < z < \frac{l}{\alpha} - (k+j)\left(l - \frac{l}{\alpha}\right), \end{cases}$$

for all $0 \leq j \in \mathbb{Z}$. Replacing z with $l - gt$, we find

$$F_2(l - gt) = \begin{cases} \lambda^j G\left(l - gt + j\left[l - \frac{l}{\alpha}\right]\right) & j\frac{l}{g} - (j-1)\frac{l}{g\alpha} < t < (k+j+1)\left(\frac{l}{g} - \frac{l}{g\alpha}\right), \\ \\ \lambda^j n_0\left(l - gt + j\left[l - \frac{l}{\alpha}\right]\right) & \\ +\lambda^{j+1} G\left(l - gt + (j+1)\left[l - \frac{l}{\alpha}\right]\right) & (k+j+1)\left(\frac{l}{g} - \frac{l}{g\alpha}\right) < t < (j+1)\frac{l}{g} - j\frac{l}{g\alpha}, \end{cases}$$

for all $0 \leq j \in \mathbb{Z}$. Thus, $n(l^-, t)$ may be expressed, for $t > \frac{l}{g\alpha}$

$$n(l^-, t) = n_2(l, t) = e^{-\mu t} F_2(l - gt) = e^{-Jt} p(t),$$

where

$$J = -\frac{g\alpha}{l(\alpha - 1)} \ln(\lambda) + \mu, \tag{2.7.1}$$

and $p(t)$ is the $\left(\frac{l}{g} - \frac{l}{g\alpha}\right)$-periodic function defined for $t > \frac{l}{g\alpha}$ by

$$p(t) = e^{(J-\mu)\left(t - j\left[\frac{l}{g} - \frac{l}{g\alpha}\right]\right)} h(t), \qquad j\frac{l}{g} - (j-1)\frac{l}{g\alpha} < t < (j+1)\frac{l}{g} - j\frac{l}{g\alpha}, \tag{2.7.2}$$

where $h(t)$ is defined as,

$$h(t) = \begin{cases} G\left(l - gt + j\left[l - \frac{l}{\alpha}\right]\right), & j\frac{l}{g} - (j-1)\frac{l}{g\alpha} < t < (k+j+1)\left(\frac{l}{g} - \frac{l}{g\alpha}\right), \\ \\ n_0\left(l - gt + j\left[l - \frac{l}{\alpha}\right]\right) & \\ +\frac{\alpha b}{g} G\left(l - gt + (j+1)\left[l - \frac{l}{\alpha}\right]\right), & (k+j+1)\left(\frac{l}{g} - \frac{l}{g\alpha}\right) < t < (j+1)\frac{l}{g} - j\frac{l}{g\alpha}, \end{cases}$$

$0 \leq j \in \mathbb{Z}$. The desired result has thus been proved.

The case when $\alpha = 2$

We now find the form of $p(t)$ when $\alpha = 2$.

First note that $\alpha = 2$ implies k, the greatest integer for which

$$\frac{l}{g\alpha} - k\frac{l(\alpha - 1)}{g\alpha} \geq 0,$$

is 1. Thus, the domain of definition of $G(z)$ becomes $0 < z < l/2$, with

$$G(z) = n_0(z) + \lambda n_0(z + l/2), \qquad 0 < z < \frac{l}{2},$$

where $\lambda = 2b/g$ in this case. Also, since $\alpha = 2$ and $k = 1$, the time interval

$$(k+j+1)\left(\frac{l}{g} - \frac{l}{g\alpha}\right) < t < (j+1)\frac{l}{g} - j\frac{l}{g\alpha}$$

in the piecewise definition of $p(t)$ disappears, and the resulting expression for $p(t)$ is

$$\begin{aligned} p(t) = e^{(J-\mu)\left(t - j\frac{l}{2g}\right)} & \left\{ n_0\left(l - gt + j\frac{l}{2}\right) \right. \\ & \left. + \lambda n_0\left(l - gt + (j+1)\frac{l}{2}\right) \right\}, \qquad (j+1)\frac{l}{2g} < t < (j+2)\frac{l}{2g}, \end{aligned}$$

where $0 \leq j \in \mathbb{Z}$. It is now straight-forward to check that $e^{-Jt}p(t) = n_2(l,t)$; where $n_2(l,t)$ comes from Equation (2.2.16), of the three part solution for $n(x,t)$, for $t > \frac{l}{2g}$ and $n_2(l,t) = n_2(l^-,t) = n(l^-,t)$ almost everywhere.

Chapter 3

Existence and stability results for fixed-size cell division with dispersion

In this chapter, the stability of an instance of the single-compartment model in Section 1.4, Chapter 1 is studied, where most of the coefficients of the model are constants, and the division function $B(x)$ is given by $b\delta(x-l)$. This means that cells may divide only at a critical size $x = l$. While the focus of this chapter is on the stability of the model, we require results regarding the existence of solutions to the model and their properties in order to prove the stability results. These results are presented in Section 3.4, after the results regarding stability.

3.1 Introduction

As in the previous chapters, we let $n(x,t)$ be the density of cells of size x at time t and we examine the single-compartment model from Chapter 1. If we let $B(x,t) = b\delta(x-l)$, for some constants $b, l > 0$ and let the other coefficients in the single-compartment model be constant, we have the following equation for the evolution of the size distribution $n(x,t)$:

$$\frac{\partial}{\partial t}n(x,t) = D\frac{\partial^2}{\partial x^2}n(x,t) - g\frac{\partial}{\partial x}n(x,t) + \alpha^2 b\delta(\alpha x - l)n(\alpha x,t) - b\delta(x-l)n(x,t) - \mu n(x,t), \quad (3.1.1)$$

where, as before, $g > 0$ is the growth rate of the cells, $\alpha > 1$ is the number of equally sized daughter cells produced on the division of one parent cell, $\mu \geq 0$ is the death rate of cells and $D > 0$ is the dispersion coefficient of the population, which describes the population-level effect of stochastic variation in the growth of each individual cell (See Section 1.5.3). The parameter $l > 0$ represents a fixed size at which cells may divide (as in the previous chapter). Cells cannot divide at any other size.

The model studied here (with constant coefficients D, g, μ and $B(x) = b\delta(x-l)$) has been considered as a model of plankton cell growth in [6]. However the unimodal steady size-distributions (see Figure 3.1 for example) of the model are also qualitatively similar to the unimodal DNA-distributions characteristic of *Escherichia coli* during exponential growth (see [65, Fig. 1], reproduced in this thesis in Figure 1.4; and [66, Fig. 7]). The differences between the steady size-distributions here and the DNA-distributions in [65] and [66] might be reduced by having varying coefficients $g(x)$, $\mu(x)$ and $D(x)$, but this increases the complexity of the analysis of the model significantly. Some examples of observed steady cell-volume distributions for various mammalian cells in suspension culture, with similar shape to the steady size-distributions obtained for the present model, can be found in [2].

Equation (3.1.1) is supplemented with the initial and boundary conditions given in Section 1.4. They are stated here for convenience and because the function space of the initial distribution $n_0(x)$ should be specified.

$$n(x,0) = n_0(x), \qquad n_0 \in (C \cap L^1 \cap L^\infty)[0,\infty) \tag{3.1.2}$$

$$Dn_x(x,t) - gn(x,t)|_{x=0} = 0, \tag{3.1.3}$$

$$n(x,t) \to 0, \qquad x \to \infty, \;\; t > 0 \tag{3.1.4}$$

$$n_x(x,t) \to 0, \qquad x \to \infty, \;\; t > 0. \tag{3.1.5}$$

Solutions are sought which belong to the set CD (for 'cell-division'), defined below:

Definition 3.1.1. *Let $[0,T]$ be some interval, with $T > 0$, and let $l > 0$ and $\alpha > 1$ be given. We define the set $CD[0,T]$ as follows:*
We say that $f(x,t) \in CD[0,T]$ if f has the following properties

- *$f(x,t)$ is continuous for $x \geq 0$ and $0 \leq t \leq T$.*
- *$f_t(x,t)$ is continuous for all $x \geq 0$ and $0 < t \leq T$;*
- *$f_x(x,t)$ and $f_{xx}(x,t)$ are continuous in the regions*

$$x \in [0, l/\alpha], x \in [l/\alpha, l], x \in [l, \infty),$$

and $0 < t \leq T$, where the derivatives at the end points of each interval are taken either from above or below (as appropriate). Note that $f_x(x,t)$ and $f_{xx}(x,t)$ may be discontinuous at $x = l$ and $x = l/\alpha$.

Given the importance of $CD[0,\infty)$, we also define $CD = CD[0,\infty)$.

We also expect that at every time t there will be only a finite total number of cells. That is, we desire that

$$\int_0^\infty n(x,t)\;dx < \infty$$

for all $t \geq 0$. The set of equations (3.1.1)-(3.1.5) shall be referred to henceforth as problem F. In Section 3.4, it is shown that when $n_0(x) \geq 0$ for all $x \geq 0$, there exists a non-negative solution to problem F in CD satisfying the above requirements.

For any value of μ, we may transform equation (3.1.1) to the case for $\mu = 0$ by examining $\overline{n}(x,t) = n(x,t)e^{\mu t}$. Thus, we assume $\mu = 0$ for the remainder of the chapter.

The fact that we have added a dispersion term Dn_{xx} in the model means that it is possible for cells to shrink. It is intended that D, in general, should be smaller than g by several orders of magnitude, so that the number of cells shrinking at any given time will be small. A cell might shrink due to apoptosis (cell death) or due to some other, not so drastic, cause such as diffusion of some substance from the cell into the surrounding medium.

In [6], SSD solutions to problem F were found to exist when $\alpha b > b + g$, and to satisfy the equation,

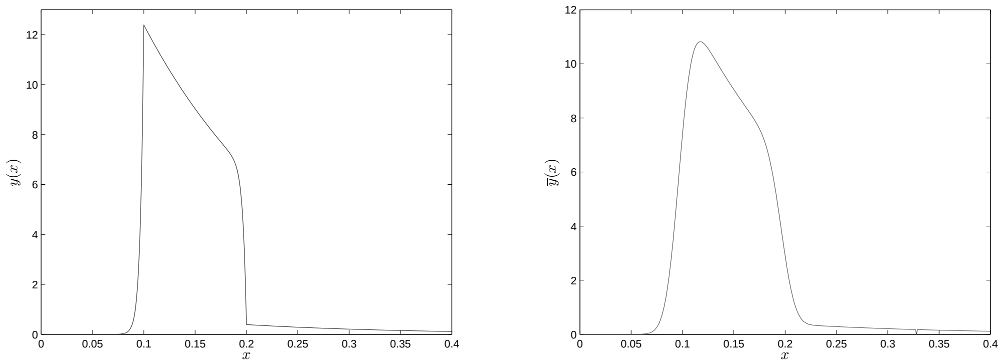
$$\begin{cases} y''(x) - \gamma y'(x) + \alpha^2\beta\delta(\alpha x - l)y(\alpha x) - (\beta\delta(x-l) + \lambda)y(x) & = 0, \\ y \in (C \cap W^{2,1} \cap L^\infty)[0,\infty), \\ y'(0) - \gamma y(0) = 0, \\ y'(x), y(x) \to 0, \qquad x \to \infty. \end{cases} \tag{3.1.6}$$

where $W^{2,1}[0,\infty)$ is the Sobolev space of functions in $L^1[0,\infty)$ with (weak) derivatives also in $L^1[0,\infty)$ up to order two and for the purposes of this chapter we treat the δ-distribution as belonging to $L^1[0,\infty)$. The coefficients γ and β are defined by: $\gamma = g/D$, $\beta = b/D$, with λ being an eigenvalue of the operator

$$y(\cdot) \to y''(\cdot) - \gamma y'(\cdot) + \alpha^2\beta\delta(\alpha\cdot - l)y(\alpha\cdot) - \beta\delta(\cdot - l)y(\cdot).$$

If such an eigenvalue exists then there is a separable solution, $N(t)y(x)$, of problem F with $N(t) = e^{\lambda Dt}$. An example SSD is given in Figure 3.1, as well as the same SSD after a smoothing integral kernel has been applied, simulating error in the observation of the distribution.

We desire to know whether these SSDs are attractors. That is: does the shape of the distribution described by the model of problem F approach an SSD as $t \to \infty$. We state the main stability theorem of this chapter below, but first we describe the dual problem to (3.1.6) and its importance.



(a) (b)

Figure 3.1: Plot (a) shows an example SSD, $y(x)$, with parameters $\alpha = 2$, $b = 50$, $g = 3$, $l = 0.2$ and $D = 0.01$. Plot (b) is a plot of the function $\overline{y}(x) = \int_0^\infty y(\xi)\mathcal{G}(\xi, x)\ d\xi$, where $\mathcal{G}(\xi, x)$ is the normal distribution with mean x and standard deviation $\sigma = 0.01$. Plot (b) simulates machine error in the measurement of the correct size-distribution from (a). Plot (b) is similar to the DNA distribution characteristic of *E. coli* during exponential growth (see [65, Fig. 1], reproduced in this thesis in Figure 1.4; and [66, Fig. 7]).

The solution ψ of the 'dual' problem to (3.1.6),

$$\begin{cases} \psi''(x) + \gamma\psi'(x) + \alpha\beta\delta(x-l)\psi\left(\frac{x}{\alpha}\right) - (\beta\delta(x-l) + \lambda)\psi(x) = 0 \\ \psi'(0) = 0, \qquad 0 < \psi(x) \in (C \cap W^{2,1} \cap L^\infty)[0,\infty), \qquad \int_0^\infty \psi(x)y(x)\ dx = 1, \end{cases} \tag{3.1.7}$$

has two very useful properties which help in proving the stability of the SSD y.

The first of these properties is given in Theorem 3.2.1, Section 3.2.2:

$$\int_0^\infty \psi(x)n(x,t)e^{-\lambda Dt}\ dx = \int_0^\infty \psi(x)n_0(x)\ dx, \qquad t \geq 0.$$

In words: the integral on the left is not dependent on time. This gives us information about the behaviour of $n(x,t)$ we did not have before, since we cannot easily find the rate of change of the overall number of cells $\int_0^\infty n(x,t)\ dx$ in time. But with the help of $\psi(x)$, we have found that the quantity $\int_0^\infty \psi(x)n(x,t)\ dx$ is proportional to $e^{\lambda Dt}$.

The second property is given in Theorem 3.2.2, Section 3.2.2; that is, for any two solutions $n(x,t)$, $v(x,t)$ of problem F corresponding to the initial distributions $n_0(x)$ and $v_0(x)$ respectively, we have:

$$\int_0^\infty \psi(x)|n(x,t_1) - v(x,t_1)|e^{-\lambda Dt_1}\ dx \leq \int_0^\infty \psi(x)|n(x,t_0) - v(x,t_0)|e^{-\lambda Dt_0}\ dx,$$

for all $0 \le t_0 < t_1$. So with the help of $\psi(x)$, we can formulate a law which, in a sense, restricts how far apart the solutions n and v may grow in any given time. Even though it may be difficult to find a general law describing how $\int_0^\infty |n(x,t) - v(x,t)|\ dx$ varies in time.

We form the dual problem (3.1.7) in the following way:

Consider (3.1.6) expressed as $\mathcal{A}y = 0$, where $\mathcal{A}$ is the appropriate differential operator. We then find the operator $\mathcal{A}^*$ such that

$$\int_0^\infty \psi(x)[\mathcal{A}y](x)\ dx = \int_0^\infty [\mathcal{A}^*\psi](x)y(x)\ dx.$$

The operator $\mathcal{A}^*$ is formed merely by integration by parts of the left-hand-side above and a substitution of variables for the term $\delta(\alpha x - l)y(\alpha x)$. The integration by parts results in an integral plus some extra terms. Letting these extra terms equal zero provides the boundary condition $\psi'(0) = 0$ in (3.1.7), while the differential equation in (3.1.7) becomes $\mathcal{A}^*\psi = 0$.

More formally, using the definitions for dual systems and adjoint (dual) operators from [43] (and presented in Appendix B): Let $\mathcal{A}$ and $\mathcal{A}^*$ be the differential operators defined above and choose X_1 to be the space of all functions $y \in (C \cap W^{2,1} \cap L^\infty)[0,\infty)$ satisfying the boundary conditions

$$y'(0) - \gamma y(0) = 0; \qquad y'(x), y(x) \to 0, \qquad x \to \infty,$$

and equipped with any norm.

Likewise choose Y_2 to be the space of all functions $\psi \in (C \cap W^{2,1} \cap L^\infty)[0,\infty)$ satisfying the boundary condition $\psi'(0) = 0$ and equipped with the same norm as that on the space X_1.

Finally, choose $X_2 = Y_1 = L^1[0,\infty)$ (where we include the δ distribution, as stated above) equipped with the standard L^1-norm and define the bilinear form $\langle\cdot,\cdot\rangle$ as

$$\langle f, g\rangle = \int_0^\infty f(x)g(x)\ dx,$$

for any $(f,g) \in X_1 \times Y_1$ or $(f,g) \in X_2 \times Y_2$. The differential operators $\mathcal{A}$ and $\mathcal{A}^*$ are then adjoint with respect to the dual systems $\langle X_1, Y_1\rangle$ and $\langle X_2, Y_2\rangle$.

The main convergence result of this chapter is expressed as follows: If we have $m(x,t) = n(x,t)e^{-\lambda D t}$, then given the existence of y and ψ described above we have, from Section 3.3,

Theorem 3.3.4. *The following convergence result holds:*

$$\int_0^\infty \psi(x)|m(x,t) - ky(x)|\ dx \to 0, \qquad t \to \infty.$$

Specifically, since $\psi(x) > 0$ for all $x \ge 0$, we find as an immediate consequence that

$$m(\cdot,t) \to ky(\cdot), \qquad t \to \infty,$$

in $L^1_{loc}[0,\infty)$. *Where*

$$k = \int_0^\infty \psi(x) m_0(x)\ dx = \int_0^\infty \psi(x) n_0(x)\ dx.$$

Thus, $m(x,t)$ tends to a constant multiple of $y(x)$ on any given finite interval. Therefore we should see the distribution $n(x,t)$ behave more and more like $e^{\lambda t} y(x)$ as t increases.

The method used here to prove the above convergence is based on [48, 49], where a 'general relative entropy' functional $\mathcal{H}$ is used, depending on time t, the solution n and the SSD/dual SSD pair y and ψ. The idea is that the functional $\mathcal{H}$ is non-negative, but has a non-positive derivative in time; therefore $\mathcal{H}$ must converge to some value. This gives us information about the behaviour of the solution n as $t \to \infty$. The nature of the cell-division terms $b\delta(x-l)$ and $\alpha^2 b\delta(\alpha x - l)$ makes the procedure developed in [49] harder to follow through, so in Section 3.3 we exploit the extra term which appears in the derivative $\mathcal{H}_t$ of the general relative entropy due to presence of dispersion ($Dn_{xx}(x,t)$) in Equation (3.1.1).

In [48, 49], among other applications of general relative entropy, the following cell growth equation is studied:

$$n_t(x,t) + n_x(x,t) + B(x)n(x,t) = \int_0^\infty b(y,x) n(y,t)\ dy,$$

with zero flux boundary condition $n(0,t) = 0$ for all $t \geq 0$. Here $b(y,x)$ represents the rate of production of cells of size x from the division of cells of size y, and

$$2B(x) = \int_0^x b(x,y)\ dy.$$

The kernel $b(x,y)$ allows asymmetric cell-division, where two unequally sized daughter cells may be produced on the division of a parent cell. Letting $b(x,y) = 2B(x)\delta(y - x/2)$ gives the case of symmetric mitosis, where two equally sized daughter cells are produced on the division of a parent cell:

$$n_t(x,t) + n_x(x,t) + B(x)n(x,t) = 4B(2x)n(2x,t).$$

A sufficient condition used in [49, Section 4] when proving the stability of the above cell-division models translates, in the case of symmetric cell-division, to $B(x)$ having infinite support. In the case of problem F, however, we have a division function $B(x) = \delta(x-l)$, which does not have infinite support. Thus, the proof of convergence in Section 3.3 exploits the extra term which arises in the derivative $\mathcal{H}_t$ due to the presence of dispersion in problem F. This extra term occurs regardless of the division function. So, potentially, the analysis of Section 3.3 could be repeated for a quite general class of division functions $B(x)$, so long as in each case the solution n, SSD

y and dual SSD ψ have similar properties to those of problem F with regards to positivity and integrability. Moreover, in [49, Section 4], the initial size-distribution is assumed to be bounded by a constant multiple of the SSD. This assumption is not needed here for Theorem 3.3.4 to hold.

In Section 3.2, we show that whenever there is an SSD $y(x)$ for a given value of λ, there also exists a dual SSD $\psi(x)$. We also prove the properties of $\psi(x)$ mentioned above in Section 3.2. Following this, in Section 3.3 we prove the important result: Theorem 3.3.4, using the general relative entropy functional $\mathcal{H}$. The analysis in Section 3.3 could be applied to the more general case where $b\delta(x-l)$ is replaced by a general function $B(x)$ assuming that the SSD, dual SSD and solution of the more general case are well-behaved enough (the necessary conditions are stated at the end of Section 3.3 and again in Section 3.5). That is, if the SSD, dual SSD and solution are such that the integrals involved in calculating $\frac{\partial}{\partial t}\mathcal{H}$ converge (See Section 3.3).

Results regarding the existence and positivity of solutions of problem F can be found in Section 3.4. The main results being:

Theorem 3.4.1. *Given initial conditions $n(x,0) = n_0(x) \in (C \cap L^1 \cap L^\infty)[0,\infty)$, there exists a unique solution $n(x,t) \in CD$ to problem F.*

Theorem 3.4.12. *Solutions of problem F with non-negative initial conditions are non-negative.*

In some places, proofs of important, yet technical results have been left until later. The proofs of these results appear in Sections 3.6-3.9.

3.2 The solution of the dual problem and its properties

In this section we first prove that whenever an SSD solution exists to problem F, satisfying the eigenvalue problem (3.1.6) for some given eigenvalue λ, then a unique solution $\psi(x)$ must exist to the dual problem (3.1.7). Following this we prove two useful properties of $\psi(x)$ that help in proving the stability of $y(x)$. Finally, we note two important bounding expressions in Equation (3.2.19) for $\psi(x)$ and the SSD $y(x)$ when $x \geq l$.

Given the relationship of the solution $\psi(x)$ of the dual problem (3.1.7) to the SSD solution $y(x)$ from (3.1.6), we refer to $\psi(x)$ as the dual SSD to $y(x)$, or simply the dual SSD in the material that follows.

First, for completeness, we write the solution of (3.1.6) given in [6]:

$$y(x) = \frac{\beta y(l)}{r_1 - r_2} \left\{ \frac{1}{r_1} \left(\alpha e^{-r_1 \frac{l}{\alpha}} - e^{-r_1 l} \right) \left(r_1 e^{r_1 x} - r_2 e^{r_2 x} \right) \right. \tag{3.2.1}$$
$$+ H(x-l) \left(e^{r_1(x-l)} - e^{r_2(x-l)} \right)$$
$$\left. -\alpha H\left(x - \frac{l}{\alpha}\right) \left(e^{r_1(x-\frac{l}{\alpha})} - e^{r_2(x-\frac{l}{\alpha})} \right) \right\},$$

where r_1 and r_2 are defined below.

3.2.1 Existence and uniqueness of the dual SSD

In [6], the Green's function for the operator $\mathcal{L}$, where $\mathcal{L}y = y'' - \gamma y' - \lambda y$, along with the boundary conditions

$$y'(0) - \gamma y(0) = 0,$$
$$y'(x), y(x) \to 0, \qquad x \to \infty$$

is considered. Here we consider the Green's function for the operator $\mathcal{L}^*$, with conditions $\psi'(0) = 0$ and $\psi \in L^\infty[0, \infty)$, where

$$\mathcal{L}^* \psi = \psi'' + \gamma \psi - \lambda \psi.$$

The characteristic equation associated with $\mathcal{L}^*$ has roots $(-\gamma \pm \sqrt{\gamma^2 + 4\lambda})/2$. These are the negatives of the roots r_1 and r_2 in [6]. For consistency, in this section we define r_1 and r_2 to be the roots from [6], where $r_1 > 0$ and $r_2 < 0$. That is

$$r_1 = \frac{\gamma + \sqrt{\gamma^2 + 4\lambda}}{2}; \qquad r_2 = \frac{\gamma - \sqrt{\gamma^2 + 4\lambda}}{2}.$$

The Green's function is then

$$G(x, \xi) = \frac{r_2 e^{r_2 \xi}}{r_1(r_1 - r_2)} \left[-\frac{r_1}{r_2} e^{-r_2 x} + e^{-r_1 x} \right] + \frac{H(x-\xi)}{r_1 - r_2} (e^{r_2(\xi - x)} - e^{r_1(\xi - x)}),$$

where H is the Heaviside function, and a formal solution to (3.1.7) is given by the expression

$$\psi(x) = \beta \left[\psi(l) - \alpha \psi\left(\frac{l}{\alpha}\right) \right] G(x, l). \tag{3.2.2}$$

We are interested only in non-trivial solutions $\psi(x)$, so $\psi(l)$ and $\psi(l/\alpha)$ must not both be equal to zero. Substituting $x = l$ and $x = l/\alpha$ into the above equation gives a pair of linear equations to solve for $\psi(l)$ and $\psi(l/\alpha)$. The system may be written as:

$$\begin{bmatrix} \beta G(l,l) - 1 & -\alpha\beta G(l,l) \\ \beta G(l/\alpha, l) & -\alpha\beta G(l/\alpha, l) - 1 \end{bmatrix} \begin{bmatrix} \psi(l) \\ \psi(l/\alpha) \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}. \tag{3.2.3}$$

For a non-trivial solution to exist, the determinant of the above matrix must be zero; that is

$$\frac{1}{\beta} = G(l,l) - \alpha G(l/\alpha, l).$$

Substituting the values for $G(l,l)$ and $G(l/\alpha,l)$ into this equation we find the following condition for a non-trivial solution to exist, namely

$$\frac{r_1(r_1-r_2)}{\beta} = r_2 e^{r_2 l}\left[-\frac{r_1}{r_2}(e^{-r_2 l} - \alpha e^{-r_2 l/\alpha}) + e^{-r_1 l} - \alpha e^{-r_1 l/\alpha}\right]. \tag{3.2.4}$$

Now, letting $\omega = -r_2$ we can reformulate the above condition into an equation involving the positive parameters α, β, γ, l and ω, giving the same condition which was obtained in [6]:

$$\begin{aligned} F(\omega) := (\gamma+\omega)(\beta+\gamma+2\omega) - \alpha\beta(\gamma+\omega)e^{-\omega l\left(1-\frac{1}{\alpha}\right)} \\ -\beta\omega e^{-\omega l}\left(\alpha e^{-(\omega+\gamma)\frac{l}{\alpha}} - e^{-(\omega+\gamma)l}\right) = 0. \end{aligned} \tag{3.2.5}$$

Solving this equation for $\omega \geq 0$ gives a possible eigenvalue λ. Assume for the moment that solutions to (3.2.5) exist. Using the first line of the linear system in (3.2.3) gives us a relationship between $\psi(l)$ and $\psi(l/\alpha)$

$$\psi(l) = \frac{-\alpha\beta\psi(l/\alpha)\Phi(l)}{1-\beta\Phi(l)}. \tag{3.2.6}$$

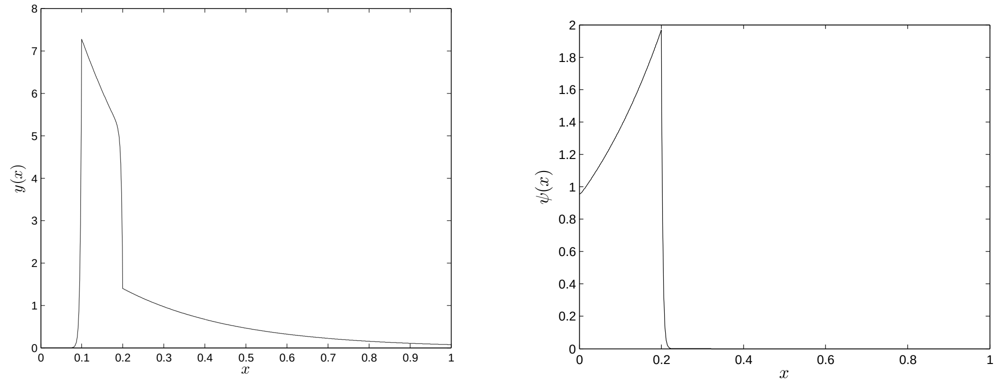
where

$$\Phi(x) = \frac{r_2 e^{r_2 l}}{r_1(r_1-r_2)}\left[-\frac{r_1}{r_2}e^{-r_2 x} + e^{-r_1 x}\right] < 0.$$

It can then be seen that if $\psi(l/\alpha) > 0$ then, according to (3.2.6), we must have $0 < \psi(l) < \alpha\psi(l/\alpha)$ and that the overall solution $\psi(x)$ must be positive. The function $\psi(x)$ which we have found is unique up to scaling. Thus, imposing the condition that $\int_0^\infty \psi(x)y(x)\,dx = 1$, we have found a solution to the dual problem (3.1.7) and the solution is unique.

The above reasoning assumed that at least one solution to (3.2.5) exists. If a solution does not exist, then neither an SSD nor a dual SSD exists. A sufficient condition for a solution ω to exist is given in [6]: $\alpha\beta > \beta + \gamma$. This ensures that the left hand side of (3.2.5) is less than zero when $\omega = 0$, and since the left hand side of (3.2.5) is continuous and tends to ∞ as $\omega \to \infty$, there is at least one $\omega > 0$ for which it is zero. In fact, the global convergence proved in the following sections shows that there can be at most one solution. An example of an SSD $y(x)$ and corresponding dual SSD $\psi(x)$ is given in Figure 3.2

The condition $\alpha\beta > \beta + \gamma$ is equivalent to the condition $\alpha b > b + g$ and essentially means that b must be large. This corresponds to cells having a high probability of dividing when they reach the size $x = l$. This should be true in most cell populations, and so is not an unrealistic restriction to impose on the model. When $\alpha b = b + g$, there exists no non-trivial SSD, since then



(a) (b)

Figure 3.2: Plot (a) shows an example SSD and (b) the dual SSD for $\alpha = 2$, $b = 8$, $g = 3$, $l = 0.2$ and $D = 0.01$. The eigenvalue was found via a bisection search for a positive root of (3.2.4). Both functions have been scaled so that $\int_0^\infty y(x)\ dx = 1$ and $\int_0^\infty y(x)\psi(x)\ dx = 1$.

$y(l)$ must be zero (by Equation (2.6) of [6]), which then forces $y(x)$ to be identically zero. In cases where $\alpha b < b + g$ the expression (3.2.5) when investigated computationally, does not appear to have positive zeros; see Figure 3.3 for two examples of $F(\omega)$ for different sets of parameters. It has not, however, been proved in this chapter that $\alpha b > b + g$ is a *necessary* condition for the existence of a SSD and dual SSD. Rather, we merely state that $\alpha b > b + g$ is *sufficient*. Further investigation is required to establish the necessity of the condition.

Note that the condition $\alpha b > b+g$ is the same condition required for a normalised hull to exist in the $D = 0$ case where we consider $\delta(x - l)n(x, t) = \delta(x - l)n(l^+, t)$ (see Section 2.4.1). Recall that in Section 2.4.1, it was stated that as $D \to 0$ the SSDs tended to the right-continuous case of the limiting SSDs (although the right and left continuous limiting SSDs were equivalent when the probability of cell-division was made equal).

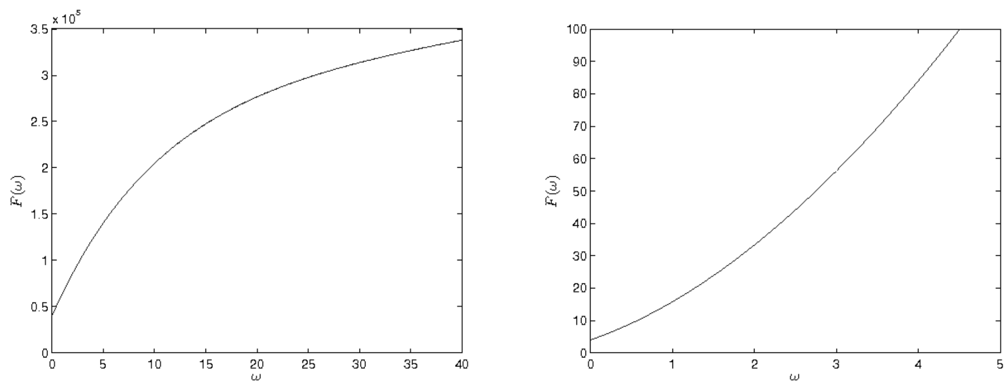
3.2.2 Some nice properties of the dual SSD

Assume that $n(x, t) \in CD$ is a solution of problem F. Given the existence of an eigenvalue λ, corresponding SSD $y(x)$ and dual SSD $\psi(x)$, which we have established above, the following two theorems hold.

Theorem 3.2.1. *The equality*

$$\int_0^\infty \psi(x)n(x, t)e^{-\lambda Dt}\ dx = \int_0^\infty \psi(x)n_0(x)\ dx$$

holds for all $t > 0$.



(a) (b)

Figure 3.3: (a) A graph of $F(\omega)$ with parameters $\alpha = 2$, $b = 3$, $g = 4$, $D = 0.01$ and $l = 0.2$ (b) A graph of $F(\omega)$ with parameters $\alpha = 2$, $b = 3$, $g = 4$, $D = 1$ and $l = 0.2$. Both of these are cases where $\alpha b < b + g$ for which there seem to be no zeros of $F(\omega)$, and hence no SSD solution of problem F.

Proof. From Theorems 3.4.5 and 3.4.8, regarding the integrability of $n(x,t)$ and $n_t(x,t)$, we find that

$$\frac{\partial}{\partial t}\psi(x)n(x,t)e^{-\lambda Dt} \in L^1([0,\infty) \times [t_0, T])$$

for any $0 < t_0 < T$. Therefore we may state that

$$\frac{\partial}{\partial t}\int_0^\infty \psi(x)n(x,t)e^{-\lambda Dt}\, dx = \int_0^\infty \psi(x)\frac{\partial}{\partial t}n(x,t)e^{-\lambda Dt}\, dx,$$

for $t > 0$ (see the application of Fubini's theorem in Section 3.6).

Integrating by parts then shows that

$$\frac{\partial}{\partial t}\int_0^\infty \psi(x)n(x,t)e^{-\lambda Dt}\, dx = 0, \tag{3.2.7}$$

for $t > 0$. Now, from Equation (3.2.2) and the expression for $G(x,\xi)$, we find that $\psi(x) \in L^1[0,\infty)$. Moreover, since $n(x,t)$ is a solution to problem F, we have $n(x,t) \in CD$, and therefore $n(x,t)e^{-\lambda Dt}$ is continuous on $[0,\infty)\times[0,\infty)$. We also find by Lemma 3.4.6, (which states that $n(x,t)$ is bounded on $[0,\infty) \times [0,T]$ for any $T > 0$) that $n(x,t)e^{-\lambda Dt} \in L^\infty([0,\infty) \times [0,T])$ for any $T > 0$.

It is now claimed that the quantity, $\int_0^\infty \psi(x)n(x,t)e^{-\lambda Dt}\, dx$, varies continuously with time. Let $t_0 \geq 0$ and $\varepsilon > 0$ be given. Then from the boundedness of $n(x,t)$ for any finite time, and the fact that $\psi(x) \in L^1[0,\infty)$, we find that there exists some $\delta > 0$ small enough, and $x^* > 0$ large enough, such that

$$\left|\int_{x^*}^\infty \psi(x)n(x,t_0)e^{-\lambda Dt_0} - n(x,t)e^{-\lambda Dt}\, dx\right| < \varepsilon,$$

for all t, with $|t - t_0| < \delta$. Moreover, due to the continuity of $n(x,t)$, we may then pick $0 < \delta' < \delta$ such that

$$\left| \int_0^{x^*} \psi(x) n(x,t_0) e^{-\lambda D t_0} - n(x,t) e^{-\lambda D t} \, dx \right| < \varepsilon.$$

We have thus shown that for any $\varepsilon > 0$ there exists some $\delta' > 0$ such that

$$\left| \int_0^{\infty} \psi(x) n(x,t_0) e^{-\lambda D t_0} - n(x,t) e^{-\lambda D t} \, dx \right| < 2\varepsilon,$$

for all t, with $|t - t_0| < \delta'$. This proves that $\int_0^\infty \psi(x) n(x,t) e^{-\lambda t} \, dx$ varies continuously with time. Therefore, since Equation (3.2.7) implies that the integral is constant for $t > 0$, it must take the same value at $t = 0$. This is the desired result. □

Theorem 3.2.2. *Let n and v be solutions to problem F with differing initial conditions $n_0(x)$ and $v_0(x)$. If $m(x,t) = n(x,t)e^{-D\lambda t}$ and $p(x,t) = v(x,t)e^{-D\lambda t}$, then*

$$\int_0^\infty \psi(x) |m(x,t_1) - p(x,t_1)| \, dx \leq \int_0^\infty \psi(x) |m(x,t_0) - p(x,t_0)| \, dx,$$

for all $t_1 > t_0 \geq 0$.

Proof. Denote $m(x,t) - p(x,t)$ by $q(x,t)$. This function satisfies

$$q_t(x,t) = Dq_{xx}(x,t) - gq_x(x,t) + \alpha^2 b\delta(\alpha x - l)q(\alpha x, t) - (b\delta(x - l) + D\lambda)q(x,t) \qquad (3.2.8)$$

and the boundary conditions (3.1.3)-(3.1.5). We now examine

$$\int_0^\infty \psi(x) |q(x,t_1)| \, dx - \int_0^\infty \psi(x) |q(x,t_0)| \, dx,$$

and show that this is less than zero. Collecting the terms under one integral sign, we find that

$$\int_0^\infty \psi(x)(|q(x,t_1)| - |q(x,t_0)|) \, dx = \int_0^\infty \psi(x) \int_{t_0}^{t_1} |q(x,t)|_t \, dt dx \qquad (3.2.9)$$

We know that q and q_t are continuous for $t > 0$ from Theorem 3.4.4. Therefore $|q|_t$ exists everywhere in $[0,\infty) \times [t_0, t_1]$ and is continuous except possibly at points where $q(x,t) = 0$. In this case either $q_t = 0$, so that $|q|_t$ is also zero, or $q_t \neq 0$, in which case $|q|_t(x,t)$ swaps sign at the point (x,t). However, when $q_t \neq 0$ it will be the case that $|q|_t(x,\tau)$ is defined for τ in a neighbourhood of t. Therefore if x is fixed and $0 < t_0 < t_1$ are any two points in time where $|q|_t$ is undefined, there will be an interval of some length within which $|q|_t$ is defined between the two points (x,t_0), (x,t_1). In other words, for fixed x there will always an interval separating two consecutive points in time where $|q|_t(x,t)$ is undefined. Each of these intervals contains a rational number and we can thus identify the set of points (for fixed x) where $|q|_t$ swaps sign, with a subset of the rational numbers. Therefore $|q|_t$ is defined almost everywhere on the region $[0, \infty) \times [t_0, t_1]$. Moreover, $|q|_t = \mathrm{sgn}(q) q_t$ almost everywhere, where

$$\mathrm{sgn}(q) = \begin{cases} 1, & q > 0, \\ 0, & q = 0, \\ -1, & q < 0. \end{cases}$$

We may then swap the order of integration in (3.2.9) due to Theorems 3.4.5 and 3.4.8, so that

$$\int_0^\infty \psi(x)(|q(x, t_1)| - |q(x, t_0)|)\ dx = \int_{t_0}^{t_1} \int_0^\infty \psi(x) \mathrm{sgn}(q(x, t)) q_t(x, t)\ dx\ dt$$

We can split the above integral with respect to x into three sections. Define

$$\int_{0, l/\alpha, l}^\infty f(x)\ dx = \int_0^{l/\alpha} f(x)\ dx + \int_{l/\alpha}^l f(x)\ dx + \int_l^\infty f(x)\ dx.$$

Then we find that

$$\begin{aligned} &\int_0^\infty \psi(x)(|q(x, t_1)| - |q(x, t_0)|)\ dx \\ = &\int_{t_0}^{t_1} \int_{0, l/\alpha, l}^\infty \psi(x) \mathrm{sgn}(q(x, t)) q_t(x, t)\ dx\ dt \\ = &\int_{t_0}^{t_1} \int_{0, l/\alpha, l}^\infty \psi(x) \mathrm{sgn}(q(x, t)) \left[D q_{xx}(x, t) - g q_x(x, t) - D\lambda q(x, t) \right]\ dx\ dt. \end{aligned}$$

Similar statements apply to $|q|_x$ as apply to $|q|_t$, in that there are a countable number of points in $[0, \infty)$ where $|q|_x$ is discontinuous (with an interval of some length between any two points where $|q|_x$ is discontinuous), and $|q|_x = \mathrm{sgn}(q) q_x$ almost everywhere. Therefore the last integral above can be expressed as

$$\int_{t_0}^{t_1} \int_{0, l/\alpha, l}^\infty \psi(x) \left[D\, \mathrm{sgn}(q(x, t)) q_{xx}(x, t) - g|q|_x(x, t) - D\lambda |q|(x, t) \right]\ dxdt. \tag{3.2.10}$$

Note that by Theorems 3.4.8, 3.4.5 and Lemma 3.4.7, we find that $\psi(\cdot)|q|_t(\cdot, t)$, $\psi(\cdot)|q|(\cdot, t)$ and $\psi(\cdot)|q|_x(\cdot, t)$ are in

$$L^1(0, l/\alpha) \cap L^1(l/\alpha, l) \cap L^1(l, \infty),$$

for any given $t > 0$. Therefore

$$\psi(\cdot) \mathrm{sgn}(q(\cdot, t)) q_{xx}(\cdot, t) \in L^1(0, l/\alpha) \cap L^1(l/\alpha, l) \cap L^1(l, \infty)$$

for any given $t > 0$.

Now, there are a countable number of points $x \in [0, \infty)$ where $q(x,t) = 0$ and $q_x(x,t) \neq 0$, with an interval of some length between any given point and the next. Call these points transition points. Consider any point which is not a transition point. When $q(x,t) \neq 0$ we have

$$\operatorname{sgn}(q(x,t))q_{xx}(x,t) = |q|_{xx}(x,t).$$

When $q(x,t) = 0$, $q_x(x,t) = 0$ there are two possibilities. The first is that $q_{xx}(x,t) = 0$, in which case

$$\lim_{h \to 0} \frac{q_x(x+h,t)}{h} = 0.$$

But this implies that

$$|q|_{xx}(x,t) = \lim_{h \to 0} \frac{|q|_x(x+h,t)}{h} = 0.$$

The second possibility is that $q_{xx} \neq 0$. In this case we must have $q(x,t)$ and $q_{xx}(x,t)$ non-zero and mono-signed in a neighbourhood of x. Thus, we may say that for almost every point x which is not a transition point of q, we have,

$$\operatorname{sgn}(q(x,t))q_{xx}(x,t) = |q|_{xx}(x,t).$$

Let x be a point where there exists a $\delta > 0$ such that $[x - \delta, x]$ contains no transition points of q, but x is the limit of a sequence of transition points larger than x. Call such a point x, an upper accumulation point. Correspondingly, call x a lower accumulation point if it is the limit of a sequence of transition points smaller than x and there exists a $\delta > 0$ such that $[x, x+\delta]$ contains no transition points. There are countably many upper and lower accumulation points.

We can now split any given interval $[a, b] \subset [0, \infty)$ into countably many subintervals in the following way (note that b is permitted to be ∞, but in this case the interval should be open at b):

- If there are no transition points in (a, b), then then we need not divide $[a, b]$ into any subintervals.

- For every transition point and lower accumulation point a_n, form the interval $[a_n, b_n]$, where b_n is the first point (greater than a_n) which is either a transition point, an upper accumulation point, or the end point, b, of the interval $[a, b]$.

- For every transition point and upper accumulation point b_n, which is not the upper endpoint of an interval already constructed form the interval $[a_n, b_n]$, where a_n is the first point (less than b_n) which is either a transition point, a lower accumulation point, or the end point, a, of the interval $[a, b]$.

Note that

$$[a,b] \setminus \bigcup_{n=1}^{\infty} [a_n, b_n]$$

consists only of points which are accumulation points (from both sides) of transition points of $q(x,t)$ and may contain the points a and b if they are upper or lower accumulation points respectively. But on those points $\text{sgn}(q(x,t)) = 0$. Consider now the integral (3.2.10). From the above reasoning, we find that:

$$\int_{0,l/\alpha,l}^{\infty} \psi(x)\text{sgn}(q(x,t))Dq_{xx}(x,t)\ dx = \sum_{n=1}^{\infty} \int_{a_n}^{b_n} \psi(x)\text{sgn}(q(x,t))Dq_{xx}(x,t)\ dx.$$

for intervals $[a_n, b_n]$ chosen as above in each of the intervals $[0, l/\alpha]$, $[l/\alpha, l]$ and $[l, \infty)$. Now, if $x \in (a_n, b_n)$ then x is not a transition point of $q(x,t)$. Therefore

$$\int_{0,l/\alpha,l}^{\infty} \psi(x)\text{sgn}(q(x,t))Dq_{xx}(x,t)\ dx = \sum_{n=1}^{\infty} \int_{a_n}^{b_n} \psi(x)D|q|_{xx}(x,t)\ dx.$$

Integrating by parts then gives

$$\int_{0,l/\alpha,l}^{\infty} \psi(x)\text{sgn}(q(x,t))Dq_{xx}(x,t)\ dx = -\int_{0,l/\alpha,l}^{\infty} \psi'(x)D|q|_x(x,t)\ dx + \sum_{n=1}^{\infty} [\psi(x)D|q|_x(x,t)]_{x=a_n}^{b_n} \tag{3.2.11}$$

We now aim to find an upper bound for the sum in the above equation.

First note that a_n and b_n are either transition points or lower/upper accumulation points. If b_n is a transition point, then it is always the case that $|q|_x(b_n,t) < 0$. Moreover, if b_n is an upper accumulation point, we must have $|q|_x(b_n,t) = 0$ (since there is a sequence of points x_k, $k = 1, 2, \ldots$ tending to b_n such that $q(x_k,t) = 0$, implying that $q_x(b_n,t) = 0$; thus $|q|_x(b_n,t) = 0$). A similar result holds if a_n is either a transition point or a lower accumulation point, except in that case $|q|_x(a_n,t) \geq 0$. Therefore we find that, for all intervals $[a_n, b_n]$ where

$$a_n, b_n \notin \{0, l/\alpha, l, \infty\},$$

we have

$$[\psi(x)D|q|_x(x,t)]_{x=a_n}^{b_n} \leq 0.$$

Now, if $b_n = l/\alpha$ for some $n \geq 1$, then there is a term $\psi(l/\alpha)D|q|_x(l/\alpha^-, t)$ in the sum in (3.2.11). If $b_n \neq l/\alpha$ for any $n \geq 1$, then l/α is the limit of a sequence transition points less than l/α, and consequently $|q|_x(l/\alpha^-, t) = 0$. Thus, even in this case we can consider that the sum in (3.2.11) contains the term

$$\psi(l/\alpha)D|q|_x(l/\alpha^-, t).$$

We can also consider whether $a_n = l/\alpha$ for any $n \geq 1$ and find that in either case the sum in (3.2.11) contains the term

$$-\psi(l/\alpha)D|q|_x(l/\alpha^+, t).$$

A similar analysis can be performed at the points $x = l$ and $x = 0$. Thus we find that

$$\sum_{n=1}^{\infty} [\psi(x)D|q|_x(x,t)]_{x=a_n}^{b_n} \leq -[\psi(x)D|q|_x(x,t)]_{l/\alpha^-}^{l/\alpha^+} - [\psi(x)D|q|_x(x,t)]_{l^-}^{l^+} - \psi(0)D|q|_x(0,t). \tag{3.2.12}$$

Let the right hand side of the above equation be denoted by $\sigma(t)$. Then, substituting (3.2.11) into (3.2.10), using the above inequality, we find

$$\begin{aligned}&\int_0^\infty \psi(x)(|q(x,t_1)| - |q(x,t_0)|)\ dx \\ &\leq \int_{t_0}^{t_1} \sigma(t) + \int_{0,l/\alpha,l}^{\infty} -\psi'(x)D|q|_x(x,t) + \psi(x)\left[-g|q|_x(x,t) - D\lambda|q|(x,t)\right]\ dx\ dt.\end{aligned}$$

Integration by parts (taking into account the fact that $\psi'(x)$ is continuous except at $x = l$ and that $\psi'(0) = 0$) then gives

$$\begin{aligned}&\int_0^\infty \psi(x)(|q(x,t_1)| - |q(x,t_0)|)\ dx \\ &\leq \int_{t_0}^{t_1} \sigma(t) + \left[\psi'(x)D|q|(x,t)\right]_{l^-}^{l^+} + \psi(0)g|q|(0,t) \\ &\qquad + \int_{0,l/\alpha,l}^{\infty} |q|(x,t)(D\psi''(x) + g\psi'(x) - D\lambda\psi(x))\ dx\ dt.\end{aligned}$$

But the integral with respect to x in the above inequality is zero (due to Equation (3.1.7)). Thus

$$\int_0^\infty \psi(x)(|q(x,t_1)| - |q(x,t_0)|)\ dx \leq \int_{t_0}^{t_1} \sigma(t) + \left[\psi'(x)D|q|(x,t)\right]_{l^-}^{l^+} + \psi(0)g|q|(0,t)\ dt. \tag{3.2.13}$$

Let us now examine the term

$$\sigma(t) + \left[\psi'(x)D|q|(x,t)\right]_{l^-}^{l^+} + \psi(0)g|q|(0,t). \tag{3.2.14}$$

Substituting in the value of $\sigma(t)$ from (3.2.12), we find that the above expression is equal to

$$-[\psi(x)D|q|_x(x,t)]_{l/\alpha^-}^{l/\alpha^+} - [\psi(x)D|q|_x(x,t)]_{l^-}^{l^+} - \psi(0)D|q|_x(0,t) + \psi(0)g|q|(0,t) + \left[\psi'(x)D|q|(x,t)\right]_{l^-}^{l^+}.$$

By the boundary condition (3.1.3), we find that the expression in (3.2.14) is equal to

$$-[\psi(x)D|q|_x(x,t)]_{l/\alpha^-}^{l/\alpha^+} - [\psi(x)D|q|_x(x,t)]_{l^-}^{l^+} + \left[\psi'(x)D|q|(x,t)\right]_{l^-}^{l^+}. \tag{3.2.15}$$

We shall now show that the above expression is less than or equal to zero. By integrating the differential equation in (3.1.7) about l, we find that

$$\left[\psi'(x)D|q|(x,t)\right]_{l^-}^{l^+} = |q|(l,t)[b\psi(l) - \alpha b\psi(l/\alpha)]. \tag{3.2.16}$$

When $q(l/\alpha, t) = 0$ it must be the case that

$$-\left[\psi(x)D|q|_x(x,t)\right]_{l/\alpha^-}^{l/\alpha^+} \leq 0,$$

since then $|q|_x(l/\alpha^-, t) \leq 0$ and $|q|_x(l/\alpha^+, t) \geq 0$. Now consider the case where $q(l/\alpha, t) \neq 0$. In this case, by integrating (3.2.8) with respect to x about the point $x = l/\alpha$, we find that

$$-\left[\psi(x)Dq_x(x,t)\right]_{l/\alpha^-}^{l/\alpha^+} = \alpha b\psi(l/\alpha)q(l,t).$$

And, in the case where $q(l/\alpha, t) \neq 0$ we have

$$\begin{aligned}
-\left[\psi(x)D|q|_x(x,t)\right]_{l/\alpha^-}^{l/\alpha^+} &= -\mathrm{sgn}(q(l/\alpha,t))\left[\psi(x)Dq_x(x,t)\right]_{l/\alpha^-}^{l/\alpha^+} \\
&= \alpha b\mathrm{sgn}(q(l/\alpha,t))q(l,t) \leq \alpha b\psi(l/\alpha)|q|(l,t).
\end{aligned}$$

In any case, therefore, we may say that

$$-\left[\psi(x)D|q|_x(x,t)\right]_{l/\alpha^-}^{l/\alpha^+} \leq \psi(l/\alpha)\alpha b|q|(l,t). \tag{3.2.17}$$

In a similar manner, we find that

$$-\left[\psi(x)D|q|_x(x,t)\right]_{l^-}^{l^+} \leq -\psi(l)b|q|(l,t). \tag{3.2.18}$$

From the inequalities (3.2.16), (3.2.17) and (3.2.18), we find that the expression in (3.2.15), is less than or equal to

$$\psi(l/\alpha)\alpha b|q|(l,t) - \psi(l)b|q|(l,t) + |q|(l,t)[b\psi(l) - \alpha b\psi(l/\alpha)].$$

But the above expression is equal to zero.

We have therefore shown that the expression in (3.2.14) is less than or equal to zero. But this implies that the right hand side of (3.2.13) is less than or equal to zero. Therefore

$$\int_0^\infty \psi(x)(|q(x,t_1)| - |q(x,t_0)|)\, dx \leq 0.$$

This is the desired result.

□

To end this section we note that from the above working and from Equation (3.2.1), we have the following two expressions for $\psi(x)$ and $y(x)$ respectively when $x \geq l$:

$$\psi(x) = C_0 e^{-r_1 x}; \qquad y(x) = C_1 e^{r_2 x}, \tag{3.2.19}$$

where C_0 and C_1 are definite constants. This fact is useful in proving the convergence of integrals involving fractions such as $\psi(x)/y(x)$.

3.3 Convergence of n to a Steady Size-Distribution solution

In this section, the central result regarding the stability of the SSDs of problem F is proved. It shall be shown that given the existence of an eigenvalue λ, a corresponding SSD $y(x)$ and dual SSD $\psi(x)$ we have

$$n(\cdot, t)e^{-D\lambda t} \to ky(\cdot)$$

in $L^1_{loc}[0,\infty)$ as $t \to \infty$, where

$$k = \int_0^\infty \psi(x)n_0(x)\ dx.$$

This main convergence result is proved in Theorem 3.3.4.

Throughout this section, let $y(x)$ and $\psi(x)$ be an SSD/dual SSD pair for problem F, satisfying (3.1.6) and (3.1.7) respectively, with corresponding eigenvalue λ. We presently make (without loss of generality) the substitution $m = ne^{-D\lambda t}$, so that y and ψ are stationary solutions to the differential equation ($m_t = \mathcal{B}m$) governing m and the dual equation ($m_t = -\mathcal{B}^* m$) respectively, where the equation governing the behaviour of m, and defining the differential operator $\mathcal{B}$, is given by

$$m_t(x,t) = Dm_{xx}(x,t) - gm_x(x,t) + \alpha^2 b\delta(\alpha x - l)m(\alpha x, t) - (b\delta(x-l) + D\lambda)m(x,t). \quad (3.3.1)$$

After first establishing Lemma 3.3.1, regarding the behaviour of $m(x,t)$ when $m_0(x)$ is bounded by a constant multiple of $y(x)$, we introduce the general relative entropy functional $\mathcal{H}(m|y,\psi)(t)$, and proceed to show that this non-negative functional is non-increasing in time. This tells us that $\mathcal{H}$ converges to some value as $t \to \infty$ and, further, that

$$\int_t^{t+T} \mathcal{H}_t(s)\ ds \to 0$$

as $t \to \infty$ for any $T > 0$. This then leads to the result given in Theorem 3.3.3:

$$\int_t^{t+T} ||m(\cdot,s) - ky(\cdot)||_{L^1[0,x_0]}\ ds \to 0, \qquad t \to \infty,$$

for any $x_0 > 0$ and, finally, to the main result in Theorem 3.3.4.

We first state the following lemma regarding the behaviour of $m(x,t)$:

Lemma 3.3.1. *If* $0 \le m_0(x) < Cy(x)$*, then* $0 \le m(x,t) < Cy(x)$ *for all* $t \ge 0$.

Note that $m_0(x) = n_0(x)$, so that if $n_0(x)$ is bounded by a constant multiple of $y(x)$, then $n(x,t)e^{-D\lambda t} = m(x,t)$ is bounded by a constant multiple of $y(x)$ for all $t \ge 0$.

Proof. Note first that (3.3.1) is linear, and that the boundary conditions that m satisfies are also linear. In Section 3.4, we prove Theorem 3.4.12, which tells us that solutions to problem F are non-negative when the initial conditions are non-negative. Therefore solutions to (3.3.1), satisfying the boundary conditions (3.1.3)-(3.1.5) from problem F, will also be non-negative when the initial conditions are non-negative.

$Cy(x) - m(x,t)$ happens to be a solution to (3.3.1) along with the boundary conditions (3.1.3)-(3.1.5). Moreover, the initial conditions for $Cy(x) - m_0(x)$ are strictly positive. Therefore $Cy(x) - m(x,t)$ is non-negative for all $t > 0$. $\square$

Following [49], we now define the general relative entropy functional $\mathcal{H} = \mathcal{H}(m|y,\psi)(t)$

$$\mathcal{H}(m|y,\psi)(t) = \int_0^\infty \psi(x)y(x)H\left(\frac{m(x,t)}{y(x)}\right)\,dx;$$

for some convex function H (by which we mean $H''(x) \geq 0$ for all $x \in \mathbb{R}$; see Definition C.0.5 in Appendix C). For the remainder of this chapter we will assume the $H(x) = x^2$. We find below that $\mathcal{H}$, a non-negative quantity, has a derivative which is non-positive.

First we note the following important identity:

Lemma 3.3.2. *The following equality holds:*

$$\mathcal{H}_t = \int_0^\infty \frac{\partial}{\partial t}\psi(x)y(x)H\left(\frac{m(x,t)}{y(x)}\right)\,dx,$$

for $t > 0$.

The proof of this theorem can be found in Section 3.6.

We shall now show that $\mathcal{H}_t \leq 0$ for all $t \geq 0$. In the first place, It may be found by a straightforward (if messy) calculation that for any convex H,

$$\begin{aligned}
&\frac{\partial}{\partial t}\left[\psi(x)y(x)H\left(\frac{m(x,t)}{y(x)}\right)\right] + g\frac{\partial}{\partial x}\left[\psi(x)y(x)H\left(\frac{m(x,t)}{y(x)}\right)\right] \\
&- D\frac{\partial}{\partial x}\left[\psi(x)^2\frac{\partial}{\partial x}\frac{y(x)}{\psi(x)}H\left(\frac{m(x,t)}{y(x)}\right)\right] + \alpha b\delta(x-l)\psi\left(\frac{x}{\alpha}\right)y(x)H\left(\frac{m(x,t)}{y(x)}\right) \\
&- \alpha^2 b\delta(\alpha x - l)\psi(x)y(\alpha x)H\left(\frac{m(\alpha x,t)}{y(\alpha x)}\right) \\
&= \alpha^2 b\delta(\alpha x - l)\psi(x)y(\alpha x)\left[H\left(\frac{m(x,t)}{y(x)}\right) - H\left(\frac{m(\alpha x,t)}{y(\alpha x)}\right)\right. \\
&\qquad \left. + H'\left(\frac{m(x,t)}{y(x)}\right)\left\{\frac{m(\alpha x,t)}{y(\alpha x)} - \frac{m(x,t)}{y(x)}\right\}\right] \\
&- D\psi(x)y(x)\left(\frac{\partial}{\partial x}\frac{m(x,t)}{y(x)}\right)^2 H''\left(\frac{m(x,t)}{y(x)}\right).
\end{aligned} \tag{3.3.2}$$

We now make use of our choice $H(x) = x^2$ for the convex function H. Integrating both sides of (3.3.2) from 0 to ∞ with respect to x with $t > 0$ gives, after applying Lemma 3.3.2 and using our choice $H(x) = x^2$,

$$\begin{aligned}\frac{d}{dt}\mathcal{H} = \alpha b\psi(l/\alpha)y(l)&\Bigg[\left(\frac{m(l/\alpha,t)}{y(l/\alpha)}\right)^2 - \left(\frac{m(l,t)}{y(l)}\right)^2 \\ &+2\left(\frac{m(l/\alpha,t)}{y(l/\alpha)}\right)\left\{\frac{m(l,t)}{y(l)} - \frac{m(l/\alpha,t)}{y(l/\alpha)}\right\}\Bigg] \\ -2\int_0^\infty D\psi(x)y(x)\left(\frac{\partial}{\partial x}\frac{m(x,t)}{y(x)}\right)^2 dx& \\ \leq 0.&\end{aligned} \tag{3.3.3}$$

The fact that $\mathcal{H}_t \leq 0$ follows from the following property of any convex function H:

$$H'(x_0)(x - x_0) \leq H(x) - H(x_0).$$

We know the integral term in Equation (3.3.3) converges by virtue of the fact that the integral of the left hand side of (3.3.2) converges when $H(x) = x^2$. To see that the integral of the left hand side of (3.3.2) converges, we make use of the expressions in (3.2.19), which tell us that the following terms all tend to zero as $x \to \infty$:

$$\frac{\psi(x)}{y(x)}, \frac{\psi'(x)}{y(x)}, \frac{\psi(x)y'(x)}{y^2(x)}; \tag{3.3.4}$$

the proof of Lemma 3.3.2 shows the integrability of the term $\frac{\partial}{\partial t}\left[\psi(x)y(x)H\left(\frac{m(x,t)}{y(x)}\right)\right]$. If we assume that $m_0(x)$ is bounded by a constant multiple of $y(x)$, then instead of using the fact that the terms from (3.3.4) tend to zero as $x \to \infty$, we require only that

$$\psi'(x)y(x) \to 0 \tag{3.3.5}$$

as $x \to \infty$, in addition to the restrictions on ψ and y which have already been imposed (such as $\psi(x) \in L^\infty[0,\infty)$ and $y(x) \to 0$ as $x \to \infty$). The final integral term in (3.3.3) only appears when dispersion is present in the model.

Now, since $\mathcal{H}$ is non-negative but $\frac{d}{dt}\mathcal{H}$ is non-positive, it must be the case that $\mathcal{H}$ tends to some limit as $t \to \infty$. This implies that for any $T > 0$,

$$\int_t^{t+T} \frac{d}{dt}\mathcal{H}(m|y,\psi)(s)\; ds \to 0, \qquad t \to \infty.$$

Specifically, with our choice $H(x) = x^2$, we find that

$$\int_t^{t+T}\int_0^{x_0} \psi(x)y(x)\left(\frac{\partial}{\partial x}\frac{m(x,s)}{y(x)}\right)^2 dxds \to 0, \qquad t \to \infty.$$

for any $x_0 > 0$. Moreover, since $\psi(x)$ and $y(x)$ are strictly positive, and applying Jensen's inequality (see Appendix C), we find that

$$\frac{1}{T}\int_t^{t+T}\frac{1}{x_0}\int_0^{x_0}\left(\frac{\partial}{\partial x}\frac{m(x,s)}{y(x)}\right)^2 dx\ ds \geq \frac{1}{T}\int_t^{t+T}\frac{1}{x_0^2}\left(\int_0^{x_0}\left|\frac{\partial}{\partial x}\frac{m(x,s)}{y(x)}\right| dx\right)^2 ds,$$

$$\geq \frac{1}{T^2x_0^2}\left(\int_t^{t+T}\int_0^{x_0}\psi(x)y(x)\left|\frac{\partial}{\partial x}\frac{m(x,s)}{y(x)}\right| dx\ ds\right)^2,$$

with the left hand side of the above inequality tending to zero as $t \to \infty$. Therefore

$$\int_t^{t+T}\int_0^{x_0}\left|\frac{\partial}{\partial x}\frac{m(x,s)}{y(x)}\right| dx\ ds \to 0, \qquad t \to \infty. \tag{3.3.6}$$

Now, consider the integral of $|m(x,t) - k(t)y(x)|$ between $x = 0$ and $x = x_0$, where $k(t) = m(0,t)/y(0)$. Manipulating this integral we obtain

$$\int_0^{x_0}|m(x,t) - k(t)y(x)|\ dx = \int_0^{x_0} y(x)\left|\frac{m(x,t)}{y(x)} - k(t)\right| dx \leq \int_0^{x_0} M\left|\frac{m(x,t)}{y(x)} - k(t)\right| dx,$$

where $M = \max_{0\leq x\leq x_0} y(x)$. But

$$\int_0^{x_0}\left|\frac{m(x,t)}{y(x)} - k(t)\right| dx = \int_0^{x_0}\left|\int_0^{x}\frac{\partial}{\partial z}\frac{m(z,t)}{y(z)}\ dz\right| dx \leq x_0\int_0^{x_0}\left|\frac{\partial}{\partial z}\frac{m(z,t)}{y(z)}\right| dz,$$

and the right hand expression integrated from t to $t+T$ tends to zero as $t \to \infty$. Therefore we see that for any $x_0 > 0$, there holds

$$\int_t^{t+T}||m(\cdot,s) - k(s)y(\cdot)||_{L^1[0,x_0]}\ ds \to 0, \qquad t \to \infty. \tag{3.3.7}$$

The following Theorem is now asserted:

Theorem 3.3.3. *For any $T > 0$,*

$$\int_t^{t+T}||m(\cdot,s) - ky(\cdot)||_{L^1[0,x_0]}\ ds \to 0, \qquad t \to \infty$$

where k is the constant defined by:

$$k = \int_0^\infty \psi(x)m_0(x)\ dx = \int_0^\infty \psi(x)m(x,t)\ dx, \qquad t > 0.$$

Proof. First note that since $y(x)$ is strictly positive and $m_0(x)$ is essentially bounded, for any $x^* > 0$ we can choose a C such that $y(x) > m_0(x)$ for all $0 \leq x \leq x^*$. Therefore it is possible to decompose $m_0(x)$ into a sum of two parts

$$m_0(x) = m_b(x) + m_u(x),$$

where $m_b(x)$ is bounded by $Cy(x)$ for some C and $m_u(x)$ is not. Specifically, for any $\varepsilon > 0$ we may choose some $x^* > 0$ such that

$$m_b(x) = m_0(x), \qquad 0 \leq x \leq x^*,$$

and $m_b(x)$ is less than a constant multiple of $y(x)$ for all $x^* < x < \infty$. Then $m_u(x) = m_0(x) - m_b(x)$, and we can make x^* large enough that

$$\int_0^\infty \psi(x) m_u(x,t)\ dx = \int_0^\infty \psi(x) m_u(x)\ dx < \varepsilon.$$

Let $m_u(x,t)$ and $m_b(x,t)$ denote the solutions for m obtained respectively from the initial conditions $m_u(x)$ and $m_b(x)$.

Now, for any $\varepsilon > 0$ it is possible to pick x^* large enough so that

$$\left|k - \int_0^{x^*} \psi(x) m(x,t)\ dx\right| = \left|\int_{x^*}^\infty \psi(x) m(x,t)\ dx\right| < \varepsilon/2T, \tag{3.3.8}$$
$$\frac{1}{1+\varepsilon} < \int_0^{x^*} \psi(x) y(x)\ dx \leq 1.$$

The second inequality may be satisfied because $\int_0^\infty \psi(x) y(x)\ dx = 1$. The first of these inequalities may be satisfied because we can decompose $m(x,t)$ into $m_b(x,t)$ and $m_u(x,t)$, so that

$$\begin{aligned}\left|\int_{x^*}^\infty \psi(x) m(x,t)\ dx\right| &\leq \left|\int_{x^*}^\infty \psi(x) m_b(x,t)\ dx\right| + \left|\int_{x^*}^\infty \psi(x) m_u(x,t)\ dx\right|, \\ &\leq \left|\int_{x^*}^\infty \psi(x) m_b(x,t)\ dx\right| + \left|\int_0^\infty \psi(x) m_u(x,t)\ dx\right|,\end{aligned}$$

with m decomposed into m_u and m_b such that

$$\left|\int_0^\infty \psi(x) m_u(x,t)\ dx\right| < \frac{\varepsilon}{4T}.$$

Then, since $m_b(x,t)$ is bounded by $Cy(x)$, we may choose x^* large enough so that

$$\left|\int_{x^*}^\infty \psi(x) m_b(x,t)\ dx\right| < \frac{\varepsilon}{4T},$$

thus satisfying the first inequality of (3.3.8)

Now, since $\psi(x)$ is bounded and the convergence from (3.3.7) holds, we may pick $t_0 > 0$ large enough so that

$$\int_t^{t+T} \int_0^{x^*} \psi(x) |m(x,s) - k(s) y(x)|\ dx ds < \frac{\varepsilon}{2}$$

for all $t \geq t_0$. But then

$$\int_t^{t+T} \left|\int_0^{x^*} \psi(x) m(x,s)\ dx - k(s) \int_0^{x^*} \psi(x) y(x)\ dx\right|\ ds < \frac{\varepsilon}{2},$$

and using the properties in (3.3.8), we find that

$$\int_t^{t+T} \left|k - \frac{k(s)}{1+\rho}\right|\ ds < \varepsilon,$$

for some $\rho < \varepsilon$ and all $t \geq t_0$. Multiplying both sides of the above inequality by $(1+\rho)$, using the triangle inequality and the fact that $\rho < \varepsilon$, we find that for any $\varepsilon > 0$ it is possible to choose some $t_0 > 0$ such that

$$\int_t^{t+T} |k - k(s)| \, ds < \varepsilon(1 + \varepsilon + kT), \qquad t \geq t_0.$$

The desired result then follows from the fact that

$$\begin{aligned}\int_t^{t+T} ||m(\cdot, s) - ky(\cdot)||_{L^1[0,x_0]} \, ds \quad &\leq \quad \int_t^{t+T} ||m(\cdot, s) - k(s)y(\cdot)||_{L^1[0,x_0]} \\ &\qquad + |k - k(s)| \int_0^{x_0} y(x) \, dx \, ds,\end{aligned}$$

for any $x_0 > 0$, where the expression on the right-hand-side tends to zero as $t \to \infty$. □

We are now ready to prove the main stability result of this chapter.

Theorem 3.3.4. *The following convergence result holds*

$$\int_0^\infty \psi(x)|m(x,t) - ky(x)| \, dx \to 0, \qquad t \to \infty. \tag{3.3.9}$$

Specifically, since $\psi(x) > 0$ for all $x \geq 0$, we find as an immediate consequence that

$$m(\cdot, t) \to ky(\cdot), \qquad t \to \infty,$$

in $L^1_{loc}[0,\infty)$. Where

$$k = \int_0^\infty \psi(x) m_0(x) \, dx = \int_0^\infty \psi(x) n_0(x) \, dx.$$

Proof. By the linearity of problem F and the positivity of y, we may decompose $m_0(x)$, in the same way as in the proof of Theorem 3.3.3, into 'bounded' and 'unbounded' components $m_b(x)$ and $m_u(x)$ such that

$$m_0(x) = m_b(x) + m_u(x),$$

where $m_b(x)$ is bounded by a constant multiple of $y(x)$ Moreover since y is strictly positive: for any $\varepsilon > 0$, we may choose $m_b(x)$ and $m_u(x)$ such that $\int_0^\infty \psi(x) m_u(x,t) \, dx < \varepsilon$ for all $t \geq 0$.

Let $m_b(x,t)$ and $m_u(x,t)$ be solutions for m obtained from the initial conditions $m_b(x)$ and $m_u(x)$ respectively and let

$$k^* = \int_0^\infty \psi(x) m_b(x) \, dx.$$

Then $|k^* - k| < \varepsilon$.

By Theorem 3.3.3, we know that

$$\int_t^{t+T} ||m_b(\cdot, s) - k^* y(\cdot)||_{L^1[0,x_0]} \to 0$$

as $t \to \infty$ for any $x_0, T > 0$. Let us assume now, by way of contradiction, that the desired result does not hold for $m_b(x,t)$. Then, since

$$\int_0^\infty \psi(x)|m_b(x,t) - k^* y(x)|\ dx$$

is non-increasing in time (by Theorem 3.2.2) we find that

$$\int_0^\infty \psi(x)|m_b(x,t) - k^* y(x)|\ dx > \varepsilon > 0, \qquad t \geq 0,$$

for some $\varepsilon > 0$.

Since $m_b(x,t) < Cy(x)$ for some $C > 0$ and all $t \geq 0$, we can choose ρ large enough such that

$$\int_\rho^\infty \psi(x)|m_b(x,t) - k^* y(x)|\ dx < \varepsilon/2.$$

Thus, there exists a $\rho > 0$ such that

$$\int_0^\rho \psi(x)|m_b(x,t) - k^* y(x)|\ dx > \varepsilon/2 > 0, \qquad t \geq 0,$$

Let M be the maximum of $\psi(x)$ for $0 \leq x \leq \rho$. Then we find that

$$\int_0^\rho |m_b(x,t) - k^* y(x)|\ dx > \frac{\varepsilon}{2M}, \qquad t \geq 0.$$

But then

$$\int_t^{t+T} ||m_b(\cdot,s) - k^* y(\cdot)||_{L^1([0,\rho])}\ ds > \frac{\varepsilon T}{2M} > 0, \qquad t \geq 0,$$

which contradicts Theorem 3.3.3. The original assumption that the desired result does not hold for $m_b(x,t)$ must therefore be incorrect.

We have now shown that the desired result holds for $m_b(x,t)$. To show that it holds for $m(x,t)$, we note that

$$\begin{aligned}\int_0^\infty \psi(x)|m(x,t) - ky(x)|\ dx \leq & \int_0^\infty \psi(x)|m_b(x,t) - k^* y(x)|\ dx \\ & + \int_0^\infty \psi(x)|m_u(x,t)|\ dx \\ & + |k^* - k| \int_0^\infty \psi(x)y(x)\ dx.\end{aligned}$$

Therefore, for any $\varepsilon > 0$ we may choose $m_b(x)$ and $m_u(x)$ as above such that

$$\lim_{t\to\infty} \int_0^\infty \psi(x)|m(x,t) - ky(x)|\ dx \leq \varepsilon.$$

But since ε may be arbitrarily small, we find that Equation (3.3.9) holds for $m(x,t)$. $\square$

We have now shown that for any given set of parameters, if an SSD solution exists to the problem F, then it is a global attractor. That is, given any non-negative initial conditions, the function $m(x,t) = n(x,t)e^{-D\lambda t}$ will tend to a constant multiple, k, of the SSD, with k given in the statement of the theorem. The fact that the convergence is global implies that there can be at most one SSD.

In the proof of Theorem 3.3.4, we needed to use Theorem 3.3.3 only for a function $m_b(x,t)$ with initial conditions $m_b(x)$ bounded by a constant multiple of $y(x)$. The fact that we could work with solutions $m_b(x,t)$ bounded by a constant multiple of $y(x)$ was a result of Lemma 3.3.1 and the fact that $y(x)$ is strictly positive. Lemma 3.3.1 was, in turn, a result of the non-negativity of the solutions $m(x,t)$ to (3.3.1) when given non-negative initial conditions.

Thus, for the above result to hold we only need the following:

- Strict positivity of $y(x)$ and $\psi(x)$, although it should be possible to weaken this assumption on $\psi(x)$, giving slightly weaker results.
- Non-negativity of solutions to problem F when the initial conditions are non-negative,
- The assumption from (3.3.5), that $\psi'(x)y(x) \to 0$ in order to calculate $\mathcal{H}_t$,
- Theorem 3.4.8, regarding the integrability of $n_t(x,t)$ (Theorem 3.4.8 leads immediately to Lemma 3.3.2 when $n(x,t)$ is bounded by a constant multiple of $y(x)$).

This is important if we wish to consider applying the analysis here to the more general problem, where we replace the δ-distributions in Equation (3.1.1) with arbitrary cell-division functions $B(x)$

3.4 Existence and properties of the solution n to problem F

Some results regarding the existence and properties of the solution n to problem F are proved in this section.

The first part of this section is devoted to proving that there is a unique solution to problem F. Theorem 3.4.1 summarises most of the results from Section 3.4.1. After Theorem 3.4.1 has been proved, we show that non-negative initial conditions $n_0(x)$ give non-negative solutions $n(x,t)$ in Section 3.4.2.

We now state the main existence theorem of this section:

Theorem 3.4.1. *Given initial conditions $n(x,0) = n_0(x) \in (C \cap L^1 \cap L^\infty)[0,\infty)$, there exists a unique solution $n(x,t) \in CD$ to problem F.*

3.4.1 Proof of Theorem 3.4.1

Here we prove results relating to the existence of solutions to problem F. The overall result from this section is expressed in Theorem 3.4.1. However, some results in this section (notably Theorems 3.4.5 and 3.4.8) are also used elsewhere, and do not only pertain to Theorem 3.4.1.

Define the function $u = ne^{-gx/2D+g^2t/4D}$. This transforms problem F to

$$\begin{cases} u_t(x,t) - Du_{xx}(x,t) = \alpha b\delta(x - l/\alpha)u(\alpha x,t)e^{\frac{g}{2D}(\alpha-1)x} & \\ \qquad\qquad\qquad\qquad - b\delta(x-l)u(x,t), & x,t>0, \\ & \\ -u_x(x,t) + \frac{g}{2D}u(x,t)|_{x=0} = 0, & t>0, \\ u(x,0) = u_0(x) = n_0(x)e^{-gx/2D}, & x>0, \end{cases} \tag{3.4.1}$$

We ignore for the moment the boundary conditions (3.1.4) and (3.1.5) on n as $x \to \infty$ (these boundary conditions are addressed in Theorem 3.4.5 and Lemma 3.4.7). We refer to this problem as problem F'.

Problem F' can be put into integral equation form using the Green's function for the homogeneous heat equation, $u_t - Du_{xx} = 0$, and the boundary condition at $x = 0$ in (3.4.1). The Green's function is given as [21],

$$\begin{aligned} G(x,t;\xi,\tau) = {} & \frac{H(t-\tau)}{2\sqrt{D\pi(t-\tau)}}\left\{\exp\left(\frac{-(x-\xi)^2}{4D(t-\tau)}\right) + \exp\left(\frac{-(x+\xi)^2}{4D(t-\tau)}\right)\right\} \\ & - H(t-\tau)\frac{g}{2D}\exp\left(\frac{g}{2D}(x+\xi) + \frac{g^2}{4D}(t-\tau)\right)\operatorname{erfc}\left[\frac{g}{2\sqrt{D}}\sqrt{t-\tau} + \frac{x+\xi}{2\sqrt{D(t-\tau)}}\right], \end{aligned} \tag{3.4.2}$$

where H is the Heaviside step function. The integral equation associated with problem F' is then,

$$\begin{aligned} u(x,t) = {} & \int_0^\infty G(x,t;\xi,0)u_0(\xi)\ d\xi \\ & + \int_0^t bu(l,\tau)[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})}G(x,t;l/\alpha,\tau) - G(x,t;l,\tau)]\ d\tau. \end{aligned} \tag{3.4.3}$$

Any solution of problem F' satisfies Equation (3.4.3).

In order to find a solution to (3.4.3) we examine the Volterra integral equation of the second kind formed when we let $x = l$, which is of the form

$$u(l,t) = f(t) + \int_0^t bu(l,\tau)[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})}G(l,t;l/\alpha,\tau) - G(l,t;l,\tau)]\ d\tau, \tag{3.4.4}$$

where $f(t) = \int_0^\infty G(l,t;\xi,0)u_0(\xi)\ d\xi$.

The function $G(x,t;\xi,0)$ is greater than or equal to zero for all $x,t,\xi,\tau > 0$. This is shown via the following bound on $\operatorname{erfc}(x)$ [62]:

$$\operatorname{erfc}(x) \leq \frac{2}{\sqrt{\pi}}\frac{e^{-x^2}}{x + \sqrt{x^2 + \frac{4}{\pi}}} < \frac{e^{-x^2}}{\sqrt{\pi}x}, \qquad x > 0. \tag{3.4.5}$$

Using this bound on the erfc term in (3.4.2) gives

$$\begin{aligned}0 \leq & \frac{H(t-\tau)}{2\sqrt{D\pi(t-\tau)}}\left\{\exp\left(\frac{-(x-\xi)^2}{4D(t-\tau)}\right)-\exp\left(\frac{-(x+\xi)^2}{4D(t-\tau)}\right)\right\} \\ \leq & G(x,t,\xi,\tau) \\ \leq & \frac{H(t-\tau)}{2\sqrt{D\pi(t-\tau)}}\left\{\exp\left(\frac{-(x-\xi)^2}{4D(t-\tau)}\right)+\exp\left(\frac{-(x+\xi)^2}{4D(t-\tau)}\right)\right\}.\end{aligned} \tag{3.4.6}$$

We now state a theorem regarding the existence of solutions $u(l,t)$ to (3.4.4).

Theorem 3.4.2. *Let* $f(t) = \int_0^\infty G(l,t;\xi,0)u_0(\xi)\, d\xi$ *and let* $k(t)$ *be the convolution kernel*

$$k(t) = \alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})}G(l,t;l/\alpha,0) - G(l,t;l,0),$$

in (3.4.4). *Then* $k(t)$ *is continuous for* $t > 0$, *with* $|k(t)| = O(1/\sqrt{t})$ *and for small enough* $T > 0$

$$u(l,t) = f(t) + \int_0^t R(t-\tau)f(\tau)\, d\tau \tag{3.4.7}$$

is the unique solution of (3.4.4) *for* $0 < t \leq T$ *where* $R(t) = k(t) + \int_0^t k(t-\tau)R(\tau)\, d\tau$ *is the resolvent kernel and* $|R(t)| = O(1/\sqrt{t})$.

The proof of this theorem is in Section 3.9. We find also the following regarding the differentiability of $u(l,t)$.

Lemma 3.4.3. $u(l,t)$ *is continuously differentiable with respect to* t *for all* $0 < t \leq T$.

Proof. Differentiating the expression (3.4.7) with respect to t gives the result:

$$u_t(l,t) = f'(t) + f(0)R(t) + \int_0^t R(t-\tau)f'(\tau)\, d\tau,$$

which is continuous for $t > 0$, since $f'(t)$ is continuous for $t > 0$ by Lemma 3.7.2. □

From the above lemma, we find that since there exists a unique $u(l,t)$ for $0 \leq t \leq T$ satisfying (3.4.4), we may obtain a full solution $u(x,t)$ to (3.4.3) for $0 \leq t \leq T$. The continuity properties of u and it's partial derivatives u_t, u_x and u_{xx} are proved in Section 3.7. These results are summarised in the following theorem:

Theorem 3.4.4. *Let* $u(x,t)$ *be the solution to* (3.4.3) *on the interval* $[0,T]$. *Then* $u(x,t)$ *is continuous for* $x \geq 0$, $t \geq 0$, *with continuous partial derivative* u_t *for* $t > 0$ *and continuous partial derivatives* u_x *and* u_{xx} *for all* $0 \leq x \neq l/\alpha, l$ *and* $t > 0$. *Moreover,* u_x *and* u_{xx} *are bounded as* $x \to l$ *and* $x \to l/\alpha$. *That is,* $u(x,t) \in CD[0,T]$.

It is also shown in Theorem 3.7.5, Section 3.7, that any $u(x,t)$ which solves the integral equation (3.4.3), solves problem F', with $u \in CD[0,T]$.

From this solution u we may then obtain the solution $n(x,t) \in CD[0,T]$ on $0 \leq t \leq T$ to problem F, but with the possible exception that $n(x,t)$ violates the boundary conditions (3.1.4) or (3.1.5) as $x \to \infty$. We shall now prove some results regarding the solution $n(x,t)$ that we have so far obtained, albeit only in the region $0 \leq t \leq T$.

First, a useful bound on the integral

$$\int_0^t |G(x,t;\xi,\tau)| \, d\tau,$$

is given by

$$\int_0^t G(x,t;\xi,\tau)\, d\tau \leq \sqrt{\frac{t}{D\pi}} \left\{ \exp\left(\frac{-(x-\xi)^2}{4Dt}\right) + \exp\left(\frac{-(x+\xi)^2}{4Dt}\right) \right\}. \tag{3.4.8}$$

This is found merely by using (3.4.6), taking the maximum values of the exponential terms in the integral and integrating the $1/\sqrt{t}$ term.

We now state a theorem which gives a strong result about the integrability of $n(x,t)$ and confirms that $n(x,t)$ satisfies the boundary condition (3.1.4) ($n(x,t) \to 0$ as $x \to \infty$) from problem F.

Theorem 3.4.5. *The function $|n(x,t)|$ obtained above is integrable over $(x,t) \in [0,\infty) \times [t_0,T]$ for all $0 < t_0 < T$, with $n(x,t) \to 0$ as $x \to \infty$ at any t.*

Specifically, on any region $(0,\infty) \times [t_0,T]$, where $0 < t_0 < T$ the function $|n(x,t)|$ is bounded by some function $B(x) \in (L^1 \cap L^\infty)[0,\infty)$ such that $B(x) \to 0$ as $x \to \infty$.

Proof. Let $0 < t_0 < T$ and assume that

$$u_0(x) e^{\frac{gx}{2D}} \in L^1[0,\infty),$$

which is the case when $n_0(x) \in L^1[0,\infty)$. It must be shown that the solution for $u(x,t)$ as expressed in (3.4.3) satisfies $\int_{t_0}^T \int_0^\infty |u(x,t)| e^{gx/2D}\, dxdt < \infty$, for the solution $n(x,t)$ of (3.1.1) to be in $L^1([0,\infty) \times [t_0,T])$. Multiplying the second term in (3.4.3) by $e^{gx/2D}$ and taking absolute values gives a term less than or equal to

$$\int_0^t b|u(l,\tau)| [\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})} G(x,t;l/\alpha,\tau) + G(x,t;l,\tau)] e^{\frac{gx}{2D}}\, d\tau. \tag{3.4.9}$$

We now use the bound (3.4.8) on the integral of G with respect to τ, and the fact that $t \leq T$ in the above integrand. These two facts give us the following bound on G in the above integral:

$$\int_0^t G(x,t;\xi,\tau)\, d\tau \leq \sqrt{\frac{T}{D\pi}} \left\{ \exp\left(\frac{-(x-\xi)^2}{4DT}\right) + \exp\left(\frac{-(x+\xi)^2}{4DT}\right) \right\}.$$

Denote the right hand side of the above inequality by $R(x, \xi)$. Using this bound and performing the integration with respect to τ, we find that the term in (3.4.9) is less than or equal to

$$Mbe^{\frac{gx}{2D}}[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})}R(x, l/\alpha) + R(x, l)], \tag{3.4.10}$$

where $M = \max_{0 \le t \le t_0+T} |u(l, t)|$. The integral of this expression with respect to x and t in the region $[0, \infty) \times [t_0, T]$ converges. Moreover the expression in (3.4.10) regarded as a function of x is in $(C \cap L^1 \cap L^\infty)[0, \infty)$, tends to zero as $x \to \infty$, and provides a bounding function for the expression in (3.4.9).

Consider now the first term of (3.4.3). Multiplying this by $e^{gx/2D}$ gives (by using the upper bound on G from (3.4.6)) a value less than or equal to

$$\int_0^\infty \frac{1}{2\sqrt{D\pi t}} \left\{ \exp\left(\frac{-(x-\xi)^2}{4Dt}\right) + \exp\left(\frac{-(x+\xi)^2}{4Dt}\right) \right\} \exp\left(\frac{g(x-\xi)}{2D}\right) n_0(\xi)\; d\xi. \tag{3.4.11}$$

This expression is less than or equal to a constant multiple of

$$\int_0^\infty \exp\left(\frac{-(x-\xi)^2}{4Dt}\right) \exp\left(\frac{g(x-\xi)}{2D}\right) n_0(\xi)\; d\xi,$$

when $t \in [t_0, T]$. This becomes, after a change of variable,

$$\int_{-\infty}^x \exp\left(\frac{-y^2}{4Dt} + \frac{gy}{2D}\right) n_0(x-y)\; dy. \tag{3.4.12}$$

Note that when t is restricted to $t_0 \le t \le T$ for some $0 < t_0 < T$, the exponential term in the above integral is bounded by a constant multiple of $e^{-|y|}$. Therefore the expression in (3.4.12) is bounded by

$$C \int_{-\infty}^x e^{-|y|} n_0(x-y)\; dy. \tag{3.4.13}$$

for some constant C. We must now show that

$$\int_0^\infty \int_{-\infty}^x e^{-|y|} n_0(x-y)\; dy\; dx.$$

in order to show that the expression (3.4.13) is in $L^1[0, \infty)$. But the above integral is equal to

$$\int_{-\infty}^\infty \int_y^\infty n_0(x-y) e^{-|y|}\; dx\; dy = \int_{-\infty}^\infty e^{-|y|} ||n||_1\; dy,$$

which is obviously less than ∞. Note that this means that the expression in (3.4.13), considered as a function of x, is in $L^1[0, \infty)$ and is a bounding function for the first term of (3.4.3). The integral of expression (3.4.11) with respect to x and t in the region $[0, \infty) \times [t_0, T]$ is therefore exceeded by the integral

$$C \int_{t_0}^{t_0+T} \frac{1}{2\sqrt{D\pi}} \int_{-\infty}^\infty e^{-|y|} ||n||_1\; dy\; dt = \frac{T}{2\sqrt{D\pi}} \int_{-\infty}^\infty e^{-|y|} ||n||_1\; dy,$$

for some constant $C > 0$.

We have thus determined that the expression for u in (3.4.3) is in $L^1([0,\infty) \times [t_0, T])$ when multiplied by $e^{gx/2D}$ for any $T \geq 0$. But $n(x,t) = ue^{gx/2D - g^2t/4D}$, and is therefore also in $L^1([0,\infty) \times [t_0, T])$.

We now find how to construct the bounding function $B(x)$ for $|n(x,t)|$. The expression in (3.4.10) has already been shown to act as a bounding function for the second term in the expression (3.4.3) for $u(x,t)e^{\frac{gx}{2D}}$. It is now left to examine more closely the expression in (3.4.9), which acts as a bounding function for the first term in the expression for $u(x,t)e^{\frac{gx}{2D}}$ and has already been shown to be in $L^1[0,\infty)$. We now see that it is also in $L^\infty[0,\infty)$, since the expression (3.4.9) has been shown to be bounded by (3.4.13), which in turn is bounded by

$$C \int_{-\infty}^{\infty} e^{-|y|} M \, dy,$$

where M is an upper bound of $n_0(x)$ for $x \geq 0$. Finally, the expression in (3.4.13) tends to zero as $x \to \infty$. We can see this by first expressing (3.4.13) as

$$\int_0^\infty e^{-|x-\xi|} n_0(\xi) \, d\xi$$

by a change of variables. Then, by the fact that $n_0 \in L^\infty[0,\infty)$, for any ε we may choose some $0 < \delta$ such that

$$\int_0^{x-\delta} e^{-|x-\xi|} n_0(\xi) \, d\xi + \int_{x+\delta}^{\infty} e^{-|x-\xi|} n_0(\xi) \, d\xi < \frac{\varepsilon}{2}$$

for any $x > \delta$. We may then, by the fact that $n_0(x) \to 0$ as $x \to \infty$, choose some $X > 0$ such that for all $x > X$ we have

$$\int_{x-\delta}^{x+\delta} e^{-|x-\xi|} n_0(\xi) \, d\xi < \frac{\varepsilon}{2}.$$

Adding up the above integrals shows that (3.4.13) tends to zero as $x \to \infty$.

The sum of the expressions (3.4.10) and (3.4.9) then provides a bounding function $B(x) \in (L^1 \cap L^\infty)[0,\infty)$ for $u(x,t)e^{\frac{gx}{2D}}$ such that $B(x) \to 0$. Since $n(x,t) = u(x,t)e^{\frac{gx}{2D} - \frac{g^2t}{4D}}$ we see that $B(x)$ is also a bounding function for $n(x,t)$ for $(x,t) \in [0,\infty) \times [t_0, T]$. This completes the proof of the theorem. $\square$

Note that the above result shows that $\int_0^\infty n(x,t) \, dx < \infty$ for all $t > 0$ and, given the fact that $n_0(x) \in L^1[0,\infty)$, we then find that $\int_0^\infty n(x,t) \, dx < \infty$ for all $t \geq 0$. Before proving that $n(x,t)$ also satisfies the boundary condition (3.1.5), we show that $n(x,t)$ is bounded in the region $[0,\infty) \times [0,T]$ for all $T > 0$.

Lemma 3.4.6. $n(x,t) \in L^\infty([0,\infty) \times [0,T])$ *for all* $T > 0$.

Proof. The above theorem shows that $n(x,t) \in L^\infty([0,\infty) \times [t_0, T])$ for any $0 < t_0 < T$. Now, using the bound (3.4.10) from the previous proof for the expression (3.4.9), we find that the expression (3.4.9) is bounded for all $(x,t) \in [0,\infty) \times [0,T]$. Moreover, the expression in (3.4.11) is less than or equal to

$$\int_0^\infty \frac{1}{\sqrt{D\pi t}} \exp\left(\frac{-(x-\xi)^2}{4Dt}\right) \exp\left(\frac{g(x-\xi)}{2D}\right) M \, d\xi,$$

where M is an upper bound for $n_0(x)$. For any $\delta > 0$, as $t \to \infty$ the above integral tends to

$$\int_{x-\delta}^{x+\delta} \frac{1}{\sqrt{D\pi t}} \exp\left(\frac{-(x-\xi)^2}{4Dt}\right) \exp\left(\frac{g(x-\xi)}{2D}\right) M \, d\xi,$$

uniformly for all $x \in [0,\infty)$. But, integrating the gaussian distribution in the above integral, we find that it is less than or equal to $2Me^{\frac{g\delta}{2D}}$. Therefore there is a t_0 small enough such that the expression in (3.4.11) is bounded for $0 \le t \le t_0$. From what we saw in the proof of Theorem 3.4.5, it is also bounded for $t_0 \le t \le T$. Therefore the expression in (3.4.11) is bounded for all $(x,t) \in [0,\infty) \times [0,T]$.

The sum of (3.4.9) and (3.4.11) form a bounding expression for $u(x,t)e^{\frac{gx}{2D}}$. Therefore $u(x,t)e^{\frac{gx}{2D}} \in L^\infty([0,\infty) \times [0,T])$ for any $T > 0$, and since $n(x,t) = u(x,t)e^{\frac{gx}{2D} - \frac{g^2 t}{4D}}$, the desired result holds. ☐

We now prove in the following Lemma that the boundary condition (3.1.5) ($n_x(x,t) \to 0$ as $x \to \infty$) is satisfied by our solution $n(x,t) = u(x,t)e^{gx/2D - g^2t/4D}$. Thus, we finally show that we have obtained a solution on the interval $0 \le t \le T$.

Lemma 3.4.7. *The boundary condition* (3.1.5) *is satisfied by* $n(x,t)$. *That is,* $n_x(x,t) \to 0$ *as* $x \to \infty$ *for all* $t > 0$.

Proof. We may express $n_x(x,t)$ as

$$\begin{aligned} n_x(x,t) &= u_x(x,t)e^{gx/2D - g^2t/4D} + \frac{g}{2D}u(x,t)e^{gx/2D - g^2t/4D}, \\ &= u_x(x,t)e^{gx/2D - g^2t/4D} + \frac{g}{2D}n(x,t). \end{aligned}$$

We already know that $n(x,t) \to 0$ as $x \to \infty$ for any particular time $t > 0$ from Theorem 3.4.5. Moreover it is shown in Theorem 3.7.6, Section 3.7, that $u_x(x,t)e^{gx/2D} \to 0$ as $x \to 0$ for any fixed $t > 0$. Thus, we see that $n_x(x,t) \to 0$ as $x \to \infty$ for any fixed $t > 0$. ☐

Using our solution $n(x,t)$ on the time interval $[0,T]$ we may take $n(x,t_0)$ at any time $t_0 < T$ and use this as the initial condition to problem F. This is possible, since we know that $n(x,t_0) \in$

$(C \cap L^1 \cap L^\infty)[0,\infty)$ by Theorem 3.4.5. We then obtain a unique solution to problem F up to a larger time. The above results then apply on the larger time interval and we may continue this process indefinitely to obtain a unique solution $n(x,t)$ on for $(x,t) \in [0,\infty) \times [0,\infty)$. In this way we find the unique solution required by Theorem 3.4.1.

We now prove a theorem regarding the integrability of $n_t(x,t)$ which allows us to state that

$$\frac{d}{dt}\int_0^\infty \psi(x)y(x)H\left(\frac{m(x,t)}{y(x)}\right)\,dx = \int_0^\infty \frac{\partial}{\partial t}\psi(x)y(x)H\left(\frac{m(x,t)}{y(x)}\right)\,dx,$$

and to equate other such pairs of expressions where the order of the integral and differential operators are swapped.

Theorem 3.4.8. *$n_t(x,t) \in L^1([0,\infty)\times[t_0,T])$ for any $0 < t_0 < T$. Moreover, for any $0 < t_0 < T$ there is a bounding function $B(x) \in L^1[0,\infty)$ with $n_t(x,t) < B(x)$ for $t \in [t_0,T]$.*

Proof. Let $0 < t_0 < T$ First note that

$$n_t(x,t) = u_t(x,t)e^{gx/2D - g^2t/4D} - (g^2t/4D)n(x,t).$$

It has already been established in Theorem 3.4.1 that $n(x,t) \in L^1([0,\infty)\times[t_0,T])$, and that there exists a bounding function for $n(x,t)$ on $[0,\infty)\times[t_0,T]$. Thus the same can be said of $\frac{g^2t}{4D}n(x,t)$. It remains, therefore, to examine $u_t(x,t)e^{gx/2D-g^2t/4D}$.

The general derivative of u is found by differentiating equation (3.4.3):

$$\begin{aligned} u_t(x,t) = &\int_0^\infty G_t(x,t;\xi,0)u_0(\xi)\,d\xi + bu(l,0^+)[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})}G(x,t;l/\alpha,0) - G(x,t;l,0)] \\ &+ \int_0^t bu_\tau(l,\tau)[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})}G(x,t;l/\alpha,\tau) - G(x,t;l,\tau)]\,d\tau. \end{aligned}$$

The integrability of the third term of the above expression (when multiplied by $e^{gx/2D}$) follows in the same way as in the proof of Theorem 3.4.5; while the integral of the second term when multiplied by $e^{gx/2D}$ follows using the estimates in Equation (3.4.6) and similar reasoning to that found in the proof of Theorem 3.4.5. Moreover the existence of a bounding function for the second and third terms also follows in a similar way as in the proof of Theorem 3.4.5. It therefore remains to be seen whether or not

$$\int_{t_0}^T \int_0^\infty \left|\int_0^\infty G_t(x,t;\xi,0)n_0(\xi)e^{\frac{g(x-\xi)}{2D}}\,d\xi\right|\,dx\,dt < \infty, \tag{3.4.14}$$

and whether there is a bounding L^1 function for the term $\left|\int_0^\infty G_t(x,t;\xi,0)n_0(\xi)e^{\frac{g(x-\xi)}{2D}}\,d\xi\right|$.

Consider now $|G_t(x,t;\xi,0)|$, where $G_t(x,t;\xi,0)$ is given in Equations 3.7.2 and 3.7.3 from Section 3.7. Using the fact that we shall be integrating over $0 < t_0 \le t \le T$, it can be found that the the convergence of the integral (3.4.14) is implied by the convergence of the following integrals:

$$\int_0^\infty \int_0^\infty (x-\xi)^2 \exp\left(\frac{-(x-\xi)^2}{4D} + \frac{g(x-\xi)}{2D}\right) n_0(\xi)\ d\xi\ dx; \tag{3.4.15}$$

$$\int_0^\infty \int_0^\infty (x+\xi)^2 \exp\left(\frac{-(x+\xi)^2}{4D} + \frac{g(x-\xi)}{2D}\right) n_0(\xi)\ d\xi\ dx. \tag{3.4.16}$$

And, in a similar way to Theorem 3.4.1, using the fact that

$$\exp\left(\frac{-y^2}{4D} + \frac{gy}{2D}\right)$$

is bounded by a constant multiple of $e^{-|y|}$, we find that the integrals (3.4.15) and (3.4.16) converge. The existence of a bounding L^1 function for the term $\int_0^\infty G_t(x,t;\xi,0)n_0(\xi)e^{\frac{g(x-\xi)}{2D}}\ d\xi$ follows in a similar way to the proof of Theorem 3.4.5. □

3.4.2 Non-negative initial conditions give non-negative solutions

We turn our attention now to the question of whether solutions of problem F' are non-negative when the initial conditions $u_0(x)$ are non-negative. If this can be established, the non-negativity of solutions to problem F, given non-negative initial conditions, follows immediately from the fact that solutions n of problem F are merely transformed solutions u of problem F', with $n(x,t) = u(x,t)e^{gx/2D-g^2t/4D}$.

In Theorem 3.4.10 and its Corollary 3.4.11, we assume that the initial conditions satisfy $n_0(l/\alpha) > 0$ (and similarly $u_0(l/\alpha) > 0$), before removing this assumption in Theorem 3.4.12.

We first require the following maximum/minimum principle for our solution $u(x,t)$:

Theorem 3.4.9. *If the solution $u(x,t)$, to problem F', is positive anywhere in the region $R = [l,\infty) \times [0,T]$, then it attains its maximum over the region R on the boundary $\Gamma = \{(x,0) : x \geq l\} \cup \{(l,t) : 0 \leq t \leq T\}$. If $u(x,t)$ is negative anywhere in R then it attains its minimum over the region R on the boundary Γ.*

This is proved in Section 3.8 and is used in the proof of Theorem 3.4.10 below. We also use the fact that Equation (3.4.1) reduces to the heat equation in the interior of the regions $R_0 = [0,l/\alpha] \times [0,T]$ and $R_1 = [l/\alpha, l] \times [0,T]$, and the standard maximum/minimum principle on a finite domain for the heat equation so that we may say that the solution $u(x,t)$, to problem F', attains its maxima and minima in the regions R_0 and R_1 on the boundaries of those regions (the boundary here does not include $t = T$, $0 < x < l/\alpha$ for the region R_0; or $t = T$, $l/\alpha < x < l$ for the region R_1).

Theorem 3.4.10. *Solutions of problem F' with non-negative initial conditions $u_0(x)$ such that $u_0(l/\alpha) > 0$, are non-negative.*

Proof. The theorem shall be proved by contradiction. Assume that there is some point where $u < 0$. We shall derive a contradiction in three steps

1. There is a negative minimum occurring at $x = l/\alpha$
2. There is a point t_0 where $u(l/\alpha, t_0) = u(l, t_0) = 0$
3. A violation of the max/min principle arises in the region $[0, l/\alpha] \times [0, t_0]$.

1. There is a negative minimum occurring at $x = l/\alpha$: By the max/min principle on the unbounded domain $[l, \infty) \times [0, T]$ given in Theorem 3.4.9, as well as the standard weak max/min principle for the heat equation in the regions $[0, l/\alpha] \times [0, T]$ and $[l/\alpha, l] \times [0, T]$, we find that the solution u must take it's minimum in the region $[0, \infty) \times [0, T]$ somewhere on the lines $(0, t)$, $(l/\alpha, t)$ or (l, t) for $t \in [0, T]$. It cannot attain its minimum value at any point $(x, 0)$, $x \geq 0$, since the initial conditions are non-negative and we have assumed that u is negative somewhere. Moreover, if $u(x, t)$ is non-negative at the points $(0, t)$, $(l/\alpha, t)$ and (l, t) for $0 \leq t \leq T$, it must be non-negative everywhere, otherwise the minimum of u would be attained elsewhere.

The minimum cannot be attained along the line $(0, t)$ since the boundary condition for u at $x = 0$ implies that when $u(0, t) < 0$ we must have $u_x(0, t) < 0$, and therefore $u(0, t)$ cannot be the minimum when it is negative.

The minimum cannot be attained on the line (l, t), $t > 0$ because if we integrate the partial differential equation in problem F' with respect to x about the point (l, t), we find that

$$u_x(l^+, t) - u_x(l^-, t) = \frac{b}{D} u(l, t). \tag{3.4.17}$$

But $u_x(l^-, t)$ must be less than or equal to zero for (l, t) to be the point where u attains its minimum. From (3.4.17) it can be seen that this implies that $u_x(l^+, t) < 0$ and that therefore the max/min principle is violated in the region $x \geq l$,

We thus conclude that the minimum must be obtained at some point $(l/\alpha, t)$ and that if $u(l/\alpha, t) \geq 0$ for $0 \leq t \leq T$, then u is non-negative on all of $[0, \infty) \times [0, T]$. Integrating the partial differential equation from problem F' (Equation 3.4.1) about $x = l/\alpha$ in the same way as above, we find that

$$u_x\left(\frac{l}{\alpha}^+, t\right) - u_x\left(\frac{l}{\alpha}^-, t\right) = -\frac{\alpha b}{D} u(l, t) e^{\frac{gl}{2D}(1 - 1/\alpha)}. \tag{3.4.18}$$

Now, since u attains its minimum at $(l/\alpha, t)$ we must have $u_x(l/\alpha^-, t) \leq 0$ and $u_x(l/\alpha^+, t) \geq 0$. We then see from (3.4.18) that it is necessary for $u(l,t)$ to be non-positive if $(l/\alpha, t)$ is to be the point where u attains its minimum value.

2. There is a point t_0 where $u(l/\alpha, t_0) = u(l, t_0) = 0$: The assumption that $u_0(l/\alpha) > 0$ implies that $u(l/\alpha, t) > 0$ for small $t \geq 0$. Therefore, by the intermediate value theorem there must be some $t_0 > 0$ such that $u(l/\alpha, t_0) = 0$, with $u(l/\alpha, t) \geq 0$ for all $0 < t < t_0$ and $u(l/\alpha, t) < 0$ for $t > t_0$ in the neighbourhood of t_0. At the point $t = t_0$ we know that

$$u(l, t_0) \geq 0$$

since otherwise some point other than $u(l/\alpha, t)$ would be the negative minimum of u in the region $[0, \infty) \times [0, t_0]$. We also know that $u_x(l/\alpha^-, t_0) \leq 0$, since $u(x, t_0) \geq 0$ for all $x \geq 0$. But then we must have

$$u(l, t_0) \leq 0$$

since otherwise $u_x(l/\alpha^+, t_0)$ would be negative according to (3.4.18). We therefore have $0 \leq u(l, t_0) \leq 0$, which implies that $u(l, t_0) = 0$.

3. Violation of the max/min principle: Now, the points (l, t_0) and $(l/\alpha, t_0)$ are minimal points for u in the region $[0, \infty) \times [0, t_0]$. Moreover, since $u(l/\alpha, t) > 0$ for small $t > 0$, the solution, u in the region $[l/\alpha, l] \times [0, t_0]$ is not identically zero (so u is not identically consant in $[l/\alpha, l] \times (0, t_0]$). Therefore, by Theorem D.0.6 from Appendix D, we find that

$$u_x(l/\alpha^+, t_0) > 0, \qquad u_x(l^-, t_0) < 0.$$

But then Equation (3.4.18) implies that $u_x(l/\alpha^-, t_0) > 0$. This implies that there is a negative minimum of u occurring in the region $[0, l/\alpha] \times [0, t_0]$ at a point other than $x = l/\alpha$. This violates the maximum principle in the region $[0, l/\alpha] \times [0, t_0]$.

Therefore, the original assumption that there is a point where $u < 0$ must be false. $\square$

The above theorem leads immediately to the following corollary regarding the positivity of the solution for problem F:

Corollary 3.4.11. *Solutions of problem F with non-negative initial conditions $n_0(x)$ such that $n_0(l/\alpha) > 0$, are non-negative.*

We now get rid of the assumption that $n_0(l/\alpha) > 0$.

Theorem 3.4.12. *Solutions of problem F with non-negative initial conditions $n_0(x)$ are non-negative.*

Proof. Let $n_1(x,t)$ be the solution to problem F arising from the initial conditions $n_0(x)$, and let $n_2(x,t)$ be the solution to problem F arising from the initial conditions $n_0(x)+Cy(x)$, where $y(x)$ is an SSD solution to problem F, solving (3.1.6), with corresponding eigenvalue λ, and $C > 0$ is some constant. Note that problem F is linear, so that $n_2(x,t)$ is given by

$$n_2(x,t) = n_1(x,t) + Cy(x)e^{\lambda Dt}.$$

Moreover, if $n_0(x)$ is non-negative for all $x \geq 0$, then $Cy(x) + n_0(x)$ is strictly positive. We thus find that $n_2(x,t)$ is non-negative via Corollary 3.4.11. Letting $C \to 0$ then shows that $n_1(x,t) \geq 0$ for all $x, t \geq 0$. ☐

3.5 Concluding Remarks

We have studied problem F, described by Equations (3.1.1)-(3.1.5), and it has been shown that for a given set of parameters, any SSD is globally asymptotically attracting; that is, any initial distribution will give a solution which tends to the SSD. This global stability implies that there can be at most one SSD.

A sufficient condition for the existence of SSDs is given as

$$\alpha b > b + g.$$

This condition implies that there is a high probability of a cell dividing when it reaches size $x = l$, and is expected to apply to most real cell-populations. Computational experiment seems to show that there is no SSD when $\alpha b < b + g$; while in the case where $\alpha b = b + g$ there is no non-trivial SSD (by Equation (2.6) of [6]).

It should be noted that most of the analysis in Section 3.3 could be applied in the case where a general division function $B(x)$ was used in the place of $b\delta(x - l)$. The main points which need to be established are as follows (from the end of Section 3.3):

- Strict positivity of $y(x)$ and $\psi(x)$, although it should be possible to weaken this assumption on $\psi(x)$, giving slightly weaker results.
- The assumption from (3.3.5), that $\psi'(x)y(x) \to 0$,
- Theorem 3.4.8, regarding the integrability of $n_t(x,t)$.

The last two points are needed in order to show that $\mathcal{H}_t \le 0$. (Theorem 3.4.8 leads immediately to Lemma 3.3.2 when $n(x,t)$ is bounded by a constant multiple of $y(x)$)

In the present case, where $B(x) = b\delta(x-l)$, an estimate of the probability of cell division when passing through $x = l$ is given by:

$$\frac{(\text{added flux at } x = l/\alpha)/\alpha}{\text{flux into } x = l}.$$

The added flux at $x = l/\alpha$ comes from daughter cells produced by cell division at $x = l$ and is found by integrating Equation (3.1.1) about $x = l/\alpha$. We then find that

$$-Dn_x\left(\frac{l}{\alpha}^+, t\right) + gn\left(\frac{l}{\alpha}, t\right) = -Dn_x\left(\frac{l}{\alpha}^-, t\right) + gn\left(\frac{l}{\alpha}, t\right) + \alpha bn(l.t).$$

Therefore the added flux from cell division is $\alpha bn(l,t)$. But this flux is due to some definite number k of growing cells, and was therefore the result of k/α cell divisions. Thus $\alpha bn(l,t)$ is α times the total flux of cells which divide as they pass through $x = l$. The probability of cell division has thus been found to be

$$\frac{bn(l,t)}{\text{flux into } x = l}$$

Let f denote the flux into $x = l$. Then

$$f = \begin{cases} -Dn_x(l^-,t) + gn(l,t), & -Dn_x(l^-,t) + gn(l,t) > 0, Dn_x(l^+,t) - gn(l,t) \le 0, \\ Dn_x(l^+,t) - gn(l,t), & -Dn_x(l^-,t) + gn(l,t) \le 0, Dn_x(l^+,t) - gn(l,t) > 0, \\ Dn_x(l^+,t) - Dn_x(l^-,t), & -Dn_x(l^-,t) + gn(l,t) > 0, Dn_x(l^+,t) - gn(l,t) > 0. \end{cases}$$

One of the three cases above must hold, since if we integrate Equation (3.1.1) about $x = l$ we find that

$$bn(l,t) = [-Dn_x(l^-,t) + gn(l,t)] + [Dn_x(l^+,t) - gn(l,t)]. \tag{3.5.1}$$

Therefore, when $n(l,t) > 0$ at least one of the terms $[-Dn_x(l^-,t)+gn(l,t)]$ or $[Dn_x(l^+,t)-gn(l,t)]$ must be positive. When $n(l,t) = 0$ we find that the derivatives $n_x(l^-,t) = n_x(l^+,t)$ and thus they must both equal zero, otherwise the solution would be negative at some point, in contradition with Theorem 3.4.12. Hence, when $n(l,t) = 0$ the flux into $x = l$ is also zero and the probability of cell division is undefined.

Note that from (3.5.1) we have $Dn_x(l^+,t) - Dn_x(l^-,t) = bn(l,t)$. Therefore we find that

$$f = \begin{cases} -Dn_x(l^+,t) + (b+g)n(l,t), & -Dn_x(l^-,t) + gn(l,t) > 0, Dn_x(l^+,t) - gn(l,t) \le 0, \\ Dn_x(l^-,t) + (b-g)n(l,t), & -Dn_x(l^-,t) + gn(l,t) \le 0, Dn_x(l^+,t) - gn(l,t) > 0, \\ bn(l,t), & -Dn_x(l^-,t) + gn(l,t) > 0, Dn_x(l^+,t) - gn(l,t) > 0. \end{cases}$$

In the first case we find that since $Dn_x(l^+,t) - gn(l,t) \leq 0$, we must have the flux into $x = l$ at least $bn(l,t)$. In the second case, since $-Dn_x(l^-,t) + gn(l,t) \leq 0$, we again find that the flux into $x = l$ must be at least $bn(l,t)$. In the third case we have found that the flux into $x = l$ is exactly $bn(l,t)$. We therefore find that the probability of an individual cell dividing as in passes through $x = l$ is given by:

$$\begin{cases} \frac{b}{-D\frac{n_x(l^+,t)}{n(l,t)}+(b+g)}, & -Dn_x(l^-,t) + gn(l,t) > 0, Dn_x(l^+,t) - gn(l,t) \leq 0, \\ \frac{b}{D\frac{n_x(l^-,t)}{n(l,t)}+(b-g)}, & -Dn_x(l^-,t) + gn(l,t) \leq 0, Dn_x(l^+,t) - gn(l,t) > 0, \\ 1, & -Dn_x(l^-,t) + gn(l,t) > 0, Dn_x(l^+,t) - gn(l,t) > 0, \end{cases}$$

and this probability is, of course, less than or equal to one in all cases. If we then set b much greater than g and D very small, the probability of division approaches one.

3.6 Proof of Lemma 3.3.2

Proof of Lemma 3.3.2. Assume that $t > 0$. Since $H(x) = x^2$ we may write

$$\frac{\partial}{\partial t}\psi(x)y(x)H\left(\frac{m(x,t)}{y(x)}\right) = 2\frac{\psi(x)}{y(x)}m_t(x,t)m(x,t) \tag{3.6.1}$$

Note that, from the expressions in (3.2.19) for $\psi(x)$ and $y(x)$ when $x \geq l$, we know that $\psi(x)/y(x) = O(e^{-(r1+r2)x})$ and from the positivity and continuity of ψ and y, we know that $\psi(x)/y(x)$ is bounded. Moreover, in Theorem 3.4.5 it is shown that $n(x,t)$ $(= m(x,t)e^{\lambda Dt})$ is integrable over $[0,\infty) \times [t_0, T]$ for any $0 < t_0 < T$. Therefore by Theorem 3.4.8, regarding the integrability of $n_t(x,t)$, we know that $\frac{\psi(x)}{y(x)}m_t(x,t)m(x,t) \in L^1([0,\infty) \times [t_0,T])$ for any $0 < t_0 < T$. But this, in turn, implies that

$$\frac{\partial}{\partial t}\psi(x)y(x)H\left(\frac{m(x,t)}{y(x)}\right) \in L^1([0,\infty) \times [t_0,T]).$$

In fact, from Theorem 3.4.5 and Theorem 3.4.8, we may make the stronger statement that,

$$\frac{\partial}{\partial t}\psi(x)y(x)H\left(\frac{m(x,t)}{y(x)}\right)$$

is bounded by some function $B(x) \in L^1[0,\infty)$ on any region $[0,\infty) \times [t_0,T]$.

Similarly to [39] we then have, for some $t_0 < t$,

$$\begin{aligned}
\int_0^\infty \frac{\partial}{\partial t}\psi(x)y(x)H\left(\frac{m(x,t)}{y(x)}\right)\,dx &= \frac{d}{dt}\int_{t_0}^t\int_0^\infty \frac{\partial}{\partial s}\psi(x)y(x)H\left(\frac{m(x,s)}{y(x)}\right)\,dx\,ds,\\
&= \frac{d}{dt}\int_0^\infty\int_{t_0}^t \frac{\partial}{\partial s}\psi(x)y(x)H\left(\frac{m(x,s)}{y(x)}\right)\,ds\,dx \qquad \text{(Fubini)},\\
&= \frac{d}{dt}\int_0^\infty \psi(x)y(x)\left[H\left(\frac{m(x,t)}{y(x)}\right) - H\left(\frac{m(x,t_0)}{y(x)}\right)\right]\,dx,\\
&= \frac{d}{dt}\int_0^\infty \psi(x)y(x)H\left(\frac{m(x,t)}{y(x)}\right)\,dx.
\end{aligned}$$

The final equality is the desired result. $\square$

3.7 Proof of Theorem 3.4.4 and other properties of solutions to (3.4.3)

In this section we prove the results summarised in Theorem 3.4.4 as well as the fact that any $u(x,t)$ which solves (3.4.3) solves problem F' (Theorem 3.7.5) and a result regarding the behaviour of $u_x(x,t)$ as $x \to \infty$ (Theorem 3.7.6).

For the remainder of this section we assume that $u(x,t)$ is a solution of (3.4.3) in the region $(x,t) \in [0,\infty) \times [0,T]$, for some $T > 0$. We also assume that the initial conditions are of the form $u_0(x) = n_0(x)e^{-gx/2D}$, with $n_0(x) \in L^1[0,\infty)$. All of the statements in this section are assumed to apply only in the domain $[0,\infty) \times [0,T]$.

The partial derivatives of $G(x,t;\xi,\tau)$ (Equation 3.4.2) with respect to x, for $t-\tau > 0$, $x,\xi > 0$, are expressed as follows:

$$\begin{aligned}
G_x(x,t;\xi,\tau) = {} & \frac{-1}{2\sqrt{D\pi(t-\tau)}}\left\{\frac{(x-\xi)}{2D(t-\tau)}\exp\left(\frac{-(x-\xi)^2}{4D(t-\tau)}\right) + \frac{(x+\xi)}{2D(t-\tau)}\exp\left(\frac{-(x+\xi)^2}{4D(t-\tau)}\right)\right\}\\
& - \frac{g^2}{4D^2}\exp\left(\frac{g}{2D}(x+\xi) + \frac{g^2}{4D}(t-\tau)\right)\operatorname{erfc}\left[\frac{g}{2\sqrt{D}}\sqrt{t-\tau} + \frac{x+\xi}{2\sqrt{D(t-\tau)}}\right] \qquad (3.7.1)\\
& + \frac{g}{D}\cdot\frac{1}{2\sqrt{D\pi(t-\tau)}}\exp\left(\frac{-(x+\xi)^2}{4D(t-\tau)}\right)
\end{aligned}$$

$$
\begin{aligned}
DG_{xx}(x,t;\xi,\tau) = {} & \frac{-1}{4\sqrt{D\pi}(t-\tau)^{3/2}}\left\{\exp\left(\frac{-(x-\xi)^2}{4D(t-\tau)}\right)+\exp\left(\frac{-(x+\xi)^2}{4D(t-\tau)}\right)\right\} \\
& + \frac{1}{2\sqrt{D\pi(t-\tau)}}\left\{\frac{(x-\xi)^2}{4D(t-\tau)^2}\exp\left(\frac{-(x-\xi)^2}{4D(t-\tau)}\right)+\frac{(x+\xi)^2}{4D(t-\tau)^2}\exp\left(\frac{-(x+\xi)^2}{4D(t-\tau)}\right)\right\} \\
& - \frac{g^3}{8D^2}\exp\left(\frac{g}{2D}(x+\xi)+\frac{g^2}{4D}(t-\tau)\right)\operatorname{erfc}\left[\frac{g}{2\sqrt{D}}\sqrt{t-\tau}+\frac{x+\xi}{2\sqrt{D(t-\tau)}}\right] \\
& + \frac{g}{2D}\left[\frac{g}{2\sqrt{D\pi(t-\tau)}}-\frac{x+\xi}{4\sqrt{D}(t-\tau)^{3/2}}\right]\exp\left(\frac{-(x+\xi)^2}{4D(t-\tau)}\right)
\end{aligned} \tag{3.7.2}
$$

When $t-\tau<0$ both of the above partial derivatives are zero. We also have the following equation for $G_t(x,t;\xi,\tau)$:

$$
G_t(x,t;\xi,\tau) = DG_{xx}(x,t;\xi,\tau)+\delta(t-\tau)\delta(x-\xi). \tag{3.7.3}
$$

Lemma 3.7.1. *The expression*

$$
\int_0^\infty G(x,t;\xi,0)u_0(\xi)\ d\xi
$$

is continuous for $x\geq 0$, $t\geq 0$.

Proof. First we show continuity for $t>0$. Let $x',x\geq 0$ and $t',t>0$. Then

$$
\begin{aligned}
& \left|\int_0^\infty G(x',t';\xi,0)u_0(\xi)\ d\xi - \int_0^\infty G(x,t;\xi,0)u_0(\xi)\ d\xi\right| \\
\leq & \int_0^\infty |G(x',t';\xi,0)-G(x,t;\xi,0)|u_0(\xi)\ d\xi.
\end{aligned}
$$

Since $u_0\in L^\infty[0,\infty)$, we find that the right hand side of the above equation is less than or equal to

$$
M\int_0^\infty |G(x',t';\xi,0)-G(x,t;\xi,0)|\ d\xi,
$$

where $M=\text{ess-sup}_{\xi>0}u_0(\xi)$.

Let $\varepsilon>0$ and choose and $\delta>0$. Then, defining

$$
s(a,b)=M\int_a^b |G(x',t';\xi,0)-G(x,t;\xi,0)|\ d\xi,
$$

there exist $X_1\geq 0$ and $X_2>X_1$ such that

$$
s(0,X_1),s(X_2,\infty)<\varepsilon/2
$$

for all $x',t'>0$ such that $|x'-x|,|t'-t|<\delta$.

Now, since $G(x,t;\xi,0)$ is continuous for $x, \xi \geq 0$ and $t > 0$, it is uniformly continuous in the compact set $[x+\delta', 0] \times [t+\delta', t-\delta'] \times [X_1, X_2]$ for any $0 < \delta' < t$. Therefore, we may choose $0 < \delta' < \delta$ such that $s(X_1, X_2) < \varepsilon/2$ for all $x', t' > 0$ where $|x'-x|, |t'-t| < \delta'$.

We have thus shown that for any $\varepsilon > 0$ there exists a $\delta' > 0$ such that

$$\left| \int_0^\infty G(x', t'; \xi, 0) u_0(\xi)\ d\xi - \int_0^\infty G(x,t;\xi,0) u_0(\xi)\ d\xi \right| \leq s(0, X_1) + s(X_1, X_2) + s(X_2, \infty) \leq \varepsilon$$

for all $x', t' > 0$ such that $|x'-x|, |t'-t| < \delta'$. This is the desired result for $t > 0$.

We now turn to the case where $t = 0$. Consider the erfc term in the expression (3.4.2) for $G(x,t;\xi,0)$. Using the bound on erfc in (3.4.5), it can be found that as $t \to 0$ we have

$$\begin{aligned}
\frac{g}{2D} \exp\left(\frac{g}{2D}(x+\xi) + \frac{g^2 t}{4D}\right) \operatorname{erfc}\left[\frac{g\sqrt{t}}{2\sqrt{D}} + \frac{x+\xi}{2\sqrt{Dt}}\right] &\leq \frac{g}{D\sqrt{\pi}} \frac{2\sqrt{Dt}}{x+\xi+\frac{4}{\sqrt{\pi}}\sqrt{Dt}} e^{\frac{-(x+\xi)^2}{4Dt}}, \\
&\leq \frac{g}{D} \frac{\sqrt{Dt}}{2\sqrt{Dt}} e^{\frac{-\xi^2}{4Dt}}.
\end{aligned}$$

But then

$$\int_0^\infty \frac{g}{D} \frac{\sqrt{Dt}}{2\sqrt{Dt}} e^{\frac{-\xi^2}{4Dt}}\ d\xi = \frac{g}{2D}\sqrt{\pi D t}.$$

So that as $t \to 0$, we find that

$$\int_0^\infty G(x,t,\xi,0) u_0(\xi)\ d\xi \to \int_0^\infty \frac{1}{2\sqrt{D\pi t}} \left(e^{\frac{-(x-\xi)^2}{4Dt}} + e^{\frac{-(x+\xi)^2}{4Dt}} \right) u_0(\xi)\ d\xi,$$

uniformly on $x \geq 0$.

Now, if we define

$$w_0(x) = \begin{cases} u_0(x), & x \geq 0 \\ u_0(-x), & x \leq 0, \end{cases}$$

Then

$$\int_0^\infty \frac{1}{2\sqrt{D\pi t}} \left(e^{\frac{-(x-\xi)^2}{4Dt}} + e^{\frac{-(x+\xi)^2}{4Dt}} \right) u_0(\xi)\ d\xi = \int_{-\infty}^\infty \frac{1}{2\sqrt{D\pi t}} e^{\frac{-(x-\xi)^2}{4Dt}} w_0(\xi)\ d\xi.$$

Since $u_0(x)$ is continuous, we find that $w_0(x)$ is also continuous. Therefore for any $x \geq 0$ and $\epsilon > 0$, there exists some $\delta > 0$ such that, for all $x', t' \geq 0$ with $|x'-x|, t' < \delta$ we have

$$\left| \int_{-\infty}^\infty \frac{1}{2\sqrt{D\pi t}} e^{\frac{-(x-\xi)^2}{4Dt}} w_0(\xi)\ d\xi - u_0(x) \right| < \varepsilon.$$

We have thus shown the continuity of $\int_0^\infty G(x,t;\xi,0) u_0(\xi)\ d\xi$ for all $(x,t) \in [0,\infty) \times [0,T]$. ☐

Lemma 3.7.2. *The expression*

$$\int_0^\infty G(x,t;\xi,0) u_0(\xi)\ d\xi$$

has continuous partial derivatives $\frac{\partial}{\partial t}$, $\frac{\partial}{\partial x}$ *and* $\frac{\partial^2}{\partial x^2}$ *for* $x \geq 0$, $t > 0$.

Proof. It is desired to show that

$$\frac{\partial}{\partial x}\int_0^\infty G(x,t;\xi,0)u_0(\xi)\ d\xi = \int_0^\infty G_x(x,t;\xi,0)u_0(\xi)\ d\xi,$$
$$\frac{\partial^2}{\partial x^2}\int_0^\infty G(x,t;\xi,0)u_0(\xi)\ d\xi = \int_0^\infty G_{xx}(x,t;\xi,0)u_0(\xi)\ d\xi,$$
$$\frac{\partial}{\partial t}\int_0^\infty G(x,t;\xi,0)u_0(\xi)\ d\xi = \int_0^\infty G_t(x,t;\xi,0)u_0(\xi)\ d\xi,$$

A similar argument to that used in Lemma 3.7.1 can be made to establish the continuity of the expressions

$$\int_0^\infty G_x(x,t;\xi,0)u_0(\xi)\ d\xi, \qquad \int_0^\infty G_{xx}(x,t;\xi,0)u_0(\xi)\ d\xi, \qquad \int_0^\infty G_t(x,t;\xi,0)u_0(\xi)\ d\xi.$$

More strongly, via the inequality

$$||x|-|y|| \le |x-y|,$$

we find the continuity of the expressions

$$\int_0^\infty |G_x(x,t;\xi,0)|u_0(\xi)\ d\xi, \qquad \int_0^\infty |G_{xx}(x,t;\xi,0)|u_0(\xi)\ d\xi, \qquad \int_0^\infty |G_t(x,t;\xi,0)|u_0(\xi)\ d\xi.$$

Consider $\int_0^\infty G_t(x,t;\xi,0)u_0(\xi)\ d\xi$. Given the continuity of the above expressions we have, for any $0 < t, T$,

$$\begin{aligned}\int_0^\infty G_t(x,t;\xi,0)u_0(\xi)\ d\xi &= \frac{\partial}{\partial t}\int_T^t\int_0^\infty G_s(x,s;\xi,0)u_0(\xi)\ d\xi\ ds,\\ &= \frac{\partial}{\partial t}\int_0^\infty\int_T^t G_s(x,s;\xi,0)u_0(\xi)\ ds\ d\xi \qquad \text{(Fubini)},\\ &= \frac{\partial}{\partial t}\int_0^\infty [G(x,t;\xi,0)-G(x,T;\xi,0)]u_0(\xi)\ d\xi,\\ &= \frac{\partial}{\partial t}\int_0^\infty G(x,t;\xi,0)u_0(\xi)\ d\xi.\end{aligned}$$

We may swap the order of integration in the second step due to the continuity (and consequently the integrability) of the integral expression $\int_0^\infty |G_t(x,t;\xi,0)|u_0(\xi)\ d\xi$.

The results for the partial derivatives $\frac{\partial}{\partial x}$ and $\frac{\partial^2}{\partial x^2}$ follow in a similar way. □

Lemma 3.7.3. *The expression*

$$\mathcal{F}(x,t) = \int_0^t bu(l,\tau)[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})}G(x,t;l/\alpha,\tau) - G(x,t;l,\tau)]\ d\tau \tag{3.7.4}$$

is continuous for $x \ge 0$, $t \ge 0$.

Proof. First, the continuity of $\mathcal{F}$ at for all points other than $x = l$ and $x = l/\alpha$ will be proved. Take any $x_0 \ne l/\alpha, l$ and take a closed interval $[X_1, X_2]$ such that $X_1, X_2 \ne l/\alpha, l$ and $0 \le X_1 <$

$x_0 < X_2$. Likewise take any $t_0 \geq 0$ and $t_1 > t_0$. The functions $G(x, t; l/\alpha, \tau)$ and $G(x, t; l, \tau)$ may be expressed as functions of x and $t - \tau$. We shall write them now as $G(x, t-\tau; l/\alpha, 0)$ and $G(x, t-\tau; l, 0)$. These functions are continuous for

$$(x, t-\tau) \in [X_1, X_2] \times [0, t_1].$$

(The functions have removable singularities at $t - \tau = 0$). Therefore since $[X_1, X_2] \times [0, t_1]$ is compact, $G(x, t-\tau; l/\alpha, 0)$ and $G(x, t-\tau; l, 0)$ are uniformly continuous in that region.

Now consider $\mathcal{F}(x, t)$. Since the integrand in (3.7.4) is uniformly continuous in x, t and τ for $(x, t) \in [X_1, X_2] \times [0, t_1]$, $\tau \leq t$, we find that $\mathcal{F}(x, t)$ is continuous at the point (x_0, t_0).

We now turn our attention to the points $x = l$ and $x = l/\alpha$ when $t > 0$. First note that there is a non-removable singularity in $G(x, t; \xi, \tau)$ when $x = \xi$ and $t = \tau$. This singularity is, however, integrable. We shall therefore examine the approximation

$$\mathcal{F}^\rho(x, t) = \int_0^{t-\rho} bu(l, \tau)[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})} G(x, t; l/\alpha, \tau) - G(x, t; l, \tau)]\; d\tau,$$

for some small $\rho > 0$.

Let there be given some $\varepsilon > 0$ and a point (x_0, t_0), where $x_0 = l$ or l/α and $t_0 > 0$. Then we may choose $\delta > 0$ and $\rho > 0$ such that for all $|t - t_0|, |x - x_0| < \delta$ we have

$$|\mathcal{F}^\rho(x, t) - \mathcal{F}(x, t)| < \varepsilon/3,$$
$$|\mathcal{F}^\rho(x, t) - \mathcal{F}^\rho(x_0, t_0)| < \varepsilon/3,$$
$$|\mathcal{F}^\rho(x_0, t_0) - \mathcal{F}(x_0, t_0)| < \varepsilon/3.$$

From this we may then conclude that $|\mathcal{F}(x, t) - \mathcal{F}(x_0, t_0)| < \varepsilon$. This proves continuity at the points $x = l$ and $x = l/\alpha$ for $t > 0$. To prove continuity at $t = 0$ when $x = l$ or $x = l/\alpha$, we again use the integrability of the singularity in $G(x, t; \xi, \tau)$ when $x = \xi$ and $t = \tau$. Thus, letting $x_0 = l$ or l/α and $t_0 = 0$, we find that given and $\varepsilon > 0$ we can choose a $\delta > 0$ such that for all $|t|, |x - x_0| < \delta$ we have

$$|\mathcal{F}(x, t) - \mathcal{F}(x, 0)| = |\mathcal{F}(x, t) - \mathcal{F}(x_0, 0)| = |\mathcal{F}(x, t)| < \varepsilon.$$

□

Lemma 3.7.4. *The expression*

$$\mathcal{F}(x, t) = \int_0^{t} bu(l, \tau)[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})} G(x, t; l/\alpha, \tau) - G(x, t; l, \tau)]\; d\tau$$

has continuous partial derivative $\frac{\partial}{\partial t}$ *for* $t > 0$ *and continuous partial derivatives* $\frac{\partial}{\partial x}$ *and* $\frac{\partial^2}{\partial x^2}$ *for* $0 \leq x \neq l/\alpha, l$ *and* $t > 0$.

Proof. Consider the derivative of the above integrand with respect to x. This is continuous in x and τ when $0 \le x \ne l/\alpha, l$ and therefore Leibniz's rule applies. Thus, when $0 \le x \ne l/\alpha, l$ we have

$$\frac{\partial}{\partial x}\mathcal{F}(x,t) = \int_0^t bu(l,\tau)[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})}G_x(x,t;l/\alpha,\tau) - G_x(x,t;l,\tau)]\ d\tau.$$

Consequently we have

$$\frac{\partial^2}{\partial x^2}\mathcal{F}(x,t) = \frac{\partial}{\partial x}\int_0^t bu(l,\tau)[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})}G_x(x,t;l/\alpha,\tau) - G_x(x,t;l,\tau)]\ d\tau,$$

and we find again that Leibniz's rule can be applied. Thus

$$\frac{\partial^2}{\partial x^2}\mathcal{F}(x,t) = \int_0^t bu(l,\tau)[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})}G_{xx}(x,t;l/\alpha,\tau) - G_{xx}(x,t;l,\tau)]\ d\tau, \tag{3.7.5}$$

when $0 \le x \ne l/\alpha, l$. A similar argument to that used in Lemma 3.7.3 shows that the above expressions are continuous for $t > 0$ and $0 \le x \ne l/\alpha, l$.

We now turn our attention to $\mathcal{F}_t(x,t)$. First note that since $G(x,t;\xi,\tau) = G(x,t-\tau;\xi,0)$ we have, after performing a substitution of variables,

$$\mathcal{F}(x,t) = \int_0^t bu(l,t-\tau)[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})}G(x,\tau;l/\alpha,0) - G(x,\tau;l,0)]\ d\tau$$

Taking the derivative with respect to t of the integrand above gives a continuous expression in t and τ. Thus Leibniz's rule may be applied and we find that

$$\begin{aligned}\mathcal{F}_t(x,t) = u(l,0^+)&[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})}G(x,t;l/\alpha,0) - G(x,t;l,0)] \\ &+ \int_0^t bu_t(l,t-\tau)[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})}G(x,\tau;l/\alpha,0) - G(x,\tau;l,0)]\ d\tau.\end{aligned} \tag{3.7.6}$$

The continuity of this expression is again established by a similar argument to that used in Lemma 3.7.3. □

The lemmas proved so far in this section, taken together, provide a proof of Theorem 3.4.4, since from Equation (3.4.3), we have

$$u(x,t) = \int_0^\infty G(x,t;\xi,0)u_0(\xi)\ d\xi + \mathcal{F}(x,t).$$

To end this section, we prove that u solves problem F' (Theorem 3.7.5) and that u_x is dominated by $e^{-gx/2D}$ as $x \to \infty$ (Theorem 3.7.6):

Theorem 3.7.5. *$u(x,t)$ is a solution of problem F', with $u(x,t) \to u_0(x)$ as $t \to 0$ for any $x > 0$.*

Proof. In the proofs of the above theorems it has been shown that the partial differential operators $\frac{\partial}{\partial t}$, $\frac{\partial}{\partial x}$ and $\frac{\partial^2}{\partial x^2}$ commute with the integral operators in the expression for $u(x,t)$. Moreover, from Lemmas 3.7.1 and 3.7.3, we find that $u(x,t)$ is continuous for all $(x,t) \in [0,\infty) \times [0,T]$, with $u(x,0) = u_0(x)$. The continuity of u_t for all $x \geq 0$ and $t > 0$, and the continuity of u_x and u_{xx} for all $0 \leq x \neq l, l/\alpha$ and $t > 0$, is established by Lemmas 3.7.2 and 3.7.4.

From Equation (3.4.3), we know that

$$u(x,t) = \int_0^\infty G(x,t;\xi,0)u(\xi)\ d\xi + \mathcal{F}(x,t).$$

The first term in the expression for u:

$$\int_0^\infty G(x,t;\xi,0)u_0(\xi)\ d\xi,$$

solves the heat equation in the semi-infinite region $[0,\infty)$ with zero flux boundary condition at $x = 0$. It remains to investigate $\mathcal{F}_t(x,t) - D\mathcal{F}_{xx}(x,t)$.

Consider $\mathcal{F}_t(x,t)$. Manipulating the expression for $\mathcal{F}_t(x,t)$ from (3.7.6), we get

$$\begin{aligned}
\mathcal{F}_t(x,t) &= u(l,0^+)[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})}G(x,t;l/\alpha,0) - G(x,t;l,0)] \\
&\quad + \int_0^t bu_t(l,t-\tau)[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})}G(x,\tau;l/\alpha,0) - G(x,\tau;l,0)]\ d\tau, \\
\\
&= u(l,0^+)[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})}G(x,t;l/\alpha,0) - G(x,t;l,0)] \\
&\quad + \int_0^t bu_\tau(l,\tau)[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})}G(x,t;l/\alpha,\tau) - G(x,t;l,\tau)]\ d\tau.
\end{aligned}$$

Since G involves a factor $H(t-\tau)$, where H is the Heaviside step function, we may extend the integral $\int_0^t$ etc. to $\int_0^\infty$. Doing this and integrating by parts gives us

$$\mathcal{F}_t(x,t) = -\int_0^\infty bu(l,\tau)[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})}G_\tau(x,t;l/\alpha,\tau) - G_\tau(x,t;l,\tau)]\ d\tau.$$

Now, since t and τ always appear together as $(t-\tau)$ in the expression of $G(x,t;\xi,\tau)$, we know that $G_t = -G_\tau$ at all points $(x,t;\xi,\tau)$. This then implies that,

$$\mathcal{F}_t(x,t) = \int_0^\infty bu(l,\tau)[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})}G_t(x,t;l/\alpha,\tau) - G_t(x,t;l,\tau)]\ d\tau.$$

Equation (3.7.3) can then be used to find that

$$\begin{aligned}
\mathcal{F}_t(x,t) &= D\mathcal{F}_{xx}(x,t) + \alpha b\delta(x-l/\alpha)u(l,t)e^{\frac{gl}{2D}(1-\frac{1}{\alpha})} - b\delta(x-l)u(l,t) \qquad (3.7.7)\\
&= D\mathcal{F}_{xx}(x,t) + \alpha b\delta(x-l/\alpha)u(\alpha x,t)e^{\frac{gx}{2D}(\alpha-1)} - b\delta(x-l)u(x,t).
\end{aligned}$$

That is, we have used (3.7.5) to find that $\mathcal{F}_t(x,t) = D\mathcal{F}_{xx}(x,t)$ when $0 \le x \neq l/\alpha, l$, with the extra δ-distributions arising from (3.7.3). Note that the continuity of $\mathcal{F}_t$ implies the continuity of $\mathcal{F}_{xx}$ (and consequently $\mathcal{F}_x$) from below and above at the points $x = l$ and $x = l/\alpha$. We thus find that $u_x(x,t)$ and $u_{xx}(x,t)$ are continuous in the regions

$$x \in [0, l/\alpha], \qquad x \in [l/\alpha, l], \qquad , x \in [l, \infty),$$

where the derivatives at the end points of each interval are taken from above or below. This is the final point required in order to state that $u(x,t)$ is in $CD[0,T]$, where $T > 0$ is the greatest time for which $u(x,t)$ is defined (assumed at the beginning of this section)..

Combining Equation (3.7.7) with our knowledge regarding $\int_0^\infty G(x,t;\xi,0)u_0(\xi)\, d\xi$, we may conclude that

$$u_t(x,t) = Du_{xx}(x,t) + \alpha b\delta(x - l/\alpha)u(\alpha x,t)e^{\frac{gx}{2D}(\alpha-1)} - b\delta(x-l)u(x,t).$$

It also follows from the properties of the Green's function G that

$$-u_x(x,t) + \frac{g}{2D}u(x,t)|_{x=0} = 0.$$

The desired result has thus been proved. $\square$

Theorem 3.7.6. *The expression*

$$|u_x(x,t)|e^{\frac{gx}{2D}}$$

tends to zero as $x \to \infty$ for any fixed $t > 0$. That is, as $x \to \infty$,

$$|u_x(x,t)| = o\left(e^{\frac{-gx}{2D}}\right),$$

for any fixed $t > 0$.

Proof. Examining the expression (3.7.1) for G_x and using the bound on $\mathrm{erfc}(x)$ in (3.4.5), it can be found that

$$\begin{aligned}
&|G_x(x,t;\xi,\tau)| \\
&\le \frac{C}{\sqrt{t-\tau}}\exp\left(\frac{-(x+\xi)^2}{4D(t-\tau)}\right) \\
&\quad + \frac{1}{2\sqrt{D\pi(t-\tau)}}\left\{\frac{|x-\xi|}{2D(t-\tau)}\exp\left(\frac{-(x-\xi)^2}{4D(t-\tau)}\right) + \frac{(x+\xi)}{2D(t-\tau)}\exp\left(\frac{-(x+\xi)^2}{4D(t-\tau)}\right)\right\}
\end{aligned}$$

where C is a definite constant, not written in full for the sake of brevity.

We again use the fact that $u(x,t) = \int_0^\infty G(x,t;\xi,0)u_0(\xi)\ d\xi + \mathcal{F}(x,t)$, and shall first prove that $\mathcal{F}_x(x,t)e^{gx/2D} \to 0$ as $x \to \infty$. Examining the term

$$\frac{(x-\xi)}{2D(t-\tau)} \exp\left(\frac{-(x-\xi)^2}{4D(t-\tau)}\right), \tag{3.7.8}$$

at any fixed value of $(x-\xi)$, we find that it is zero at $t-\tau = 0$, increases to a maximum at $t-\tau = \frac{(x-\xi)^2}{4D}$ and then decreases as $t-\tau \to \infty$.

But then if we fix a time t and the value of ξ, the maximum value of (3.7.8) will be obtained at $\tau = 0$ for large enough values of x.

A similar analysis can be applied to the term

$$\frac{(x+\xi)}{2D(t-\tau)} \exp\left(\frac{-(x+\xi)^2}{4D(t-\tau)}\right).$$

These results show that

$$\begin{aligned}
|\mathcal{F}_x(x,t)| &\le \int_0^t bu(l,\tau)[\alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})}|G_x(x,t;l/\alpha,\tau)| + |G_x(x,t;l,\tau)|]\ d\tau \\
&\le C_1\sqrt{t}\left[\exp\left(\frac{-(x+l)^2}{4Dt}\right) + \exp\left(\frac{-(x+l/\alpha)^2}{4Dt}\right)\right] \\
&\quad + C_2\sqrt{t}\left\{\frac{(x-l)}{2Dt}\exp\left(\frac{-(x-l)^2}{4Dt}\right) + \frac{(x+l)}{2Dt}\exp\left(\frac{-(x+l)^2}{4Dt}\right)\right\} \\
&\quad + C_2\sqrt{t}\left\{\frac{(x-l/\alpha)}{2Dt}\exp\left(\frac{-(x-l/\alpha)^2}{4Dt}\right) + \frac{(x+l/\alpha)}{2Dt}\exp\left(\frac{-(x+l/\alpha)^2}{4Dt}\right)\right\},
\end{aligned}$$

where C_1 and C_2 are definite constants depending on $\max_{0\le t\le T} u(l,t)$. From this it can be seen that $|\mathcal{F}_x(x,t)|e^{gx/2D} \to 0$ as $x \to \infty$.

The proof that $\int_0^\infty |G_x(x,t;\xi,0)|u_0(\xi)e^{gx/2D}\ d\xi \to 0$ as $x \to \infty$ is similar to the proof that the first term of (3.4.3), when multiplied by $e^{gx/2D}$ tends to zero as $x \to \infty$; this is proved as part of Theorem 3.4.5. $\square$

3.8 Unbounded maximum/minimum principles

In this section we prove two results. The first, Theorem 3.8.1, gives a general maximum/minimum principle for the heat equation on a semi-infinite domain. The proof is based on the proof of Theorem 6 from Section 2.3.3 of [24]. Theorem 3.4.9, which gives a more specific maximum principle on a semi-infinite domain for solutions of problem F' in Section 3.4 is also proved here. These results are almost certainly not new. However, we provide a proof here for completeness.

Theorem 3.8.1. *Let $u(x,t)$ solve the homogeneous heat equation*

$$u_t(x,t) = Du_{xx}(x,t),$$

for $(x,t) \in R = (0,\infty) \times (0,T]$ *and let* u *have continuous partial derivatives* u_t*,* u_x *and* u_{xx} *in* R*. Assume moreover that* u *is continuous on* $\overline{R} = [0,\infty) \times [0,T]$ *and that* u *is bounded in* $\overline{R}$*. Let* $\Gamma = \overline{R} \setminus R$*. Then*

$$\sup_{(x,t)\in\overline{R}} u(x,t) = \sup_{(x,t)\in\Gamma} u(x,t).$$

And, similarly

$$\inf_{(x,t)\in\overline{R}} u(x,t) = \inf_{(x,t)\in\Gamma} u(x,t)$$

Proof. Fix ε, δ and $y > 0$ and define

$$v(x,t) = u(x,t) - \frac{\varepsilon}{\sqrt{D(T+\delta-t)}} e^{\frac{(x-y)^2}{4D(T+\delta-t)}}.$$

A straightforward calculation shows that $v_t(x,t) = Dv_{xx}(x,t)$ for $x > 0$ and $t > 0$. Fix $X > 0$ and let Γ_X be the union of the lines

$$(x,0),\ \ 0 \le x \le X; \qquad (0,t),\ \ 0 \le t \le T, \qquad \text{and} \quad (X,t),\ \ 0 \le t \le T.$$

Then by the max/min principle for the heat equation in a bounded domain (See [24, Section 2.3.3]) we have

$$\max_{(x,t)\in[0,X]\times[0,T]} v(x,t) = \max_{(x,t)\in\Gamma_X} v(x,t). \tag{3.8.1}$$

Now, we know that

$$v(x,0) = u(x,0) - \frac{\varepsilon}{\sqrt{D(T+\delta)}} e^{\frac{(x-y)^2}{4D(T+\delta)}} \le u_0(x). \tag{3.8.2}$$

Note that $u(x,t) \in L^\infty(\overline{R})$. Let M be an upper bound for u on $\overline{R}$. Then we have

$$\begin{aligned} v(X,t) &= u(X,t) - \frac{\varepsilon}{\sqrt{D(T+\delta-t)}} e^{\frac{(X-y)^2}{4D(T+\delta-t)}} \\ &\le M - \frac{\varepsilon}{\sqrt{D(T+\delta-t)}} e^{\frac{(X-y)^2}{4D(T+\delta-t)}} \\ &\le M - \frac{\varepsilon}{\sqrt{D(T+\delta)}} e^{\frac{(X-y)^2}{4D(T+\delta)}}. \end{aligned}$$

Thus, for large enough X we have

$$v(X,t) \le \sup_{x\in[0,\infty)} u_0(x). \tag{3.8.3}$$

When $x = 0$ we have

$$v(0,t) = u(0,t) - \frac{\varepsilon}{\sqrt{D(T+\delta-t)}} e^{\frac{(0-y)^2}{4D(T+\delta-t)}} \le u(0,t). \tag{3.8.4}$$

Equations (3.8.1)-(3.8.4) imply that $v(y,t) \le \sup_{(x,t)\in\Gamma} u(x,t)$. Letting $\varepsilon \to 0$ shows that $u(y,t) \le \sup_{(x,t)\in\Gamma} u(x,t)$ for all $y \in [0,\infty)$, $t \in [0,T]$.

A similar proof can be followed to show that $u(y,t) \ge \inf_{(x,t)\in\Gamma} u(x,t)$ for all $y \in [0,\infty)$, $t \in [0,T]$. $\square$

Proof of Theorem 3.4.9. Assume that $u(x,t)$ is positive somewhere in R (defined as in the statement of Theorem 3.4.9). Note that $u(x,t)$ solves the heat equation on $R \setminus \Gamma$ and is continuous on $\overline{R}$. Thus, by Theorem 3.8.1, we know that

$$\sup_{(x,t)\in R} u(x,t) = \sup_{(x,t)\in\Gamma} u(x,t).$$

However, since $u_0(x) = n_0(x)^{-gx/2D}$, and $n_0(x)$ is bounded, we see that $u_0(x) \to 0$ as $x \to \infty$. Moreover $u_0(x) \geq 0$, for $x \geq 0$. Thus, there exists a maximal point for u on the line $t = 0$, $l \leq x \leq \infty$. Moreover since the line (l,t), $0 \leq t \leq T$, is finite and closed we find that there exists a maximal point for $u(x,t)$ on that line. Therefore $u(x,t)$ attains its maximum on Γ. Thus

$$\max_{(x,t)\in R} u(x,t) = \max_{(x,t)\in\Gamma} u(x,t).$$

In the case where $u(x,t)$ is negative somewhere in R, the proof is similar, except in that case, since $u_0(x) \geq 0$, the minimum cannot occur at $t = 0$. □

3.9 Proof of Theorem 3.4.2

Here we present a proof of Theorem 3.4.2. The theorem itself is a variation of the result from [45] for Volterra integral equations of the second kind. In this case we have a convolution kernel $k(t)$ with magnitude $O(1/\sqrt{t})$ as $t \to 0$ which is continuous at every other point $t > 0$. Before proving Theorem 3.4.2 we require the aid of the following theorem

Theorem 3.9.1. *Let $k(t)$ be continuous for $t > 0$ and let $|k(t)| = O(1/\sqrt{t})$. That is: let there exist some constant $C > 0$ such that*

$$|k(t)| \leq \frac{C}{\sqrt{t}}.$$

Then for $T > 0$ small enough, there exists a solution $R(t)$ to the integral equation,

$$R(t) = k(t) + \int_0^t k(t-\tau)R(\tau)\, d\tau. \tag{3.9.1}$$

such that $R(t)$ is continuous for $0 < t \leq T$ and $|R(t)|$ is $O(1/\sqrt{t})$.

Proof. The result shall be proved by a successive approximation argument. Let $R^0(t) = k(t)$ and let

$$R^{j+1}(t) = k(t) + \int_0^t k(t-\tau)R^j(\tau)\, d\tau$$

for all integers $j \geq 0$. Assume that $|R^j(\tau)|$ is $O(1/\sqrt{t})$ when $t \leq T$, for some $T > 0$. Then the integral

$$\int_0^t k(t-\tau)R^j(\tau)\, d\tau$$

converges for $t \leq T$. To prove this claim we split the above integral into two parts:

$$\int_0^t k(t-\tau)R^j(\tau)\ d\tau = \int_0^{t/2} k(t-\tau)R^j(\tau)\ d\tau + \int_0^{t/2} k(\tau)R^j(t-\tau)\ d\tau,$$

where the second term on the right-hand-side has been obtained by a standard substitution of variables. Consider the first term on the right-hand-side,

$$\int_0^{t/2} k(t-\tau)R^j(\tau)\ d\tau.$$

By the assumptions of the theorem we have

$$|k(t-\tau)| \leq C\sqrt{\frac{2}{t}}; \qquad \int_0^{t/2} |R^j(\tau)|\ d\tau \leq D\sqrt{2t},$$

for some positive constants C and D. Combining these two inequalities gives us

$$\left|\int_0^{t/2} k(t-\tau)R^j(\tau)\ d\tau\right| \leq 2CD < \infty,$$

for all $0 \leq t$. Similarly we find that

$$\left|\int_0^{t/2} k(\tau)R^j(t-\tau)\ d\tau\right| \leq 2CD < \infty,$$

for all $0 \leq t$. This shows that the integral $\int_0^t k(t-\tau)R^j(\tau)\ d\tau$ is bounded for all $0 \leq t \leq T$. Moreover, this implies that the difference $|R^1(t) - R^0(t)|$, which we may express as

$$|R^1(t) - R^0(t)| = \left|\int_0^t k(\tau)R^0(t-\tau)\ d\tau\right|,$$

is bounded by a constant. Therefore, choosing any $T > 0$ sufficiently small, we find that $R^1(t)$ is $O(1/\sqrt{t})$ for $0 < t \leq T$. Assume now that $R^j(t)$ and $R^{j-1}(t)$ are $O(1/\sqrt{t})$ for $0 < t \leq T$. Then the difference

$$|R^{j+1}(t) - R^j(t)| = \left|\int_0^t k(\tau)[R^j(t-\tau) - R^{j-1}(t)]\ d\tau\right|$$

exists and is bounded by a constant. Therefore $R^{j+1}(t)$ exists and is $O(1/\sqrt{t})$ for $0 < t \leq T$. The hypothesis that $R^j(t)$ and $R^{j-1}(t)$ are $O(1/\sqrt{t})$ for $0 < t \leq T$ is satisfied for $j = 1$. Therefore we find that given the initial estimate $R^0(t) = k(t)$, we can form an infinite sequence $R^j(t)$, $j = 1, 2, 3, \ldots$, of approximations to the solution of (3.9.1). We may then use a standard successive approximation argument to prove the existence of a limit for small enough $T > 0$ and the fact that it is a solution of the integral equation. $\square$

We may now prove Theorem 3.4.2:

Proof of Theorem 3.4.2. Consider the expression for $k(t)$:

$$k(t) = \alpha e^{\frac{gl}{2D}(1-\frac{1}{\alpha})} G(l, t; l/\alpha, 0) - G(l, t; l, 0)$$

Using the bounds on $G(x, t; \xi, \tau)$ in (3.4.6), we find that $G(l, t; l, 0) = O(1/\sqrt{t})$ and $G(l, t; l/\alpha, 0) \to 0$ as $t \to 0$. This implies that $|k(t)| = O(1/\sqrt{t})$ and that, by Theorem 3.9.1, the resolvent kernel $R(t)$ exists for small enough $T > 0$, with $|R(t)| = O(1/\sqrt{t})$. Since the existence of $R(t)$ has been established, the remainder of the proof of this theorem is similar to the proof of Theorem 3.5 in [45]. The solution $u(l, t)$ is unique and continuous for $0 \leq t \leq T$ by Theorem 3.2 of [45]. The five requirements of Theorem 3.2 in [45] are shown below to hold in the case of (3.4.4):

(i) $f(t)$ is continuous in $0 \leq t \leq T$,

(ii) For every continuous function h and all $0 \leq \tau_1 \leq \tau_2 \leq t$ the integrals

$$\int_{\tau_1}^{\tau_2} k(t-s)h(s)\ ds$$

and

$$\int_0^t k(t-s)h(s)\ ds$$

are continuous functions of t. This is proved using the reasoning in the proof of Lemma 3.7.3

(iii) $k(t - s)$ is absolutely integrable with respect to s for all $0 \leq t \leq T$.

(iv) There exist points $0 = T_0 < T_1 < T_2 < \cdots < T_N = T$ such that, for all i and all $T_i < t < T_{i+1}$ we have

$$\int_{T_i}^{\min(t, T_{i+1})} |k(t-s)|\ ds \leq \alpha < 1,$$

where α is independent of t and i.

(v) For every t in $[0, T]$ we have

$$\lim_{\delta \to 0^+} \int_t^{t+\delta} |k(t + \delta - s)|\ ds = 0.$$

Points (iii)-(v) follow from the fact that $k(t) = O(1/\sqrt{t})$. □

Chapter 4

Upper and lower solution method for a class of nonlocal ordinary differential equations related to the SSDs of cell-growth models

The theory described in this chapter was intended to be the foundation for a theory relating SSDs of the single compartment model with small D to the SSDs (if any) when $D = 0$. This would allow us to approximate an SSD of the single-compartment model when D is small, with the SSD when $D = 0$ (which should be easier to find). In Section 4.6 we see an application to estimating the cumulative SSD (see Section 4.6 for details) for small D of the single-compartment model with constant coefficients, but this falls short of the result which was aimed for. However, the results are general enough that they may find a use elsewhere.

Most of the material in this chapter appears in [7]. However, Section 4.7 has been added, giving results for a more general class of nonlocal differential equations. Initially we deal with differential equations having terms such as $y(\alpha x)$, which appear in the single-compartment cell-growth model in Chapter 1. Section 4.7 aims to include terms such as, for example

$$\int_I b(x, \xi) y(\xi)\ d\xi,$$

where I is some interval.

4.1 Introduction to the general problem

The general problem addressed in this chapter is expressed as follows. We desire a function $y \in C^2(I)$, on some interval I, such that

$$y'' = f(x, y, y^*, y'), \tag{4.1.1}$$

Either none, one or both of the boundary conditions

$$p_0 y(a) - q_0 y'(a) = A, \tag{4.1.2}$$

$$p_1 y(b) + q_1 y'(b) = B, \tag{4.1.3}$$

are used, depending on whether we are investigating the solution on $I = (-\infty, \infty)$, $I = [a, \infty)$ or $I = [a, b]$ respectively. Here we have $a < b \in \mathbb{R}$; p_i, q_i, $i \in \{1, 2\}$ constant, with $p_i > 0$ and $q_i \geq 0$; and y^* is a nonlocal component representing $(y \circ \lambda)(x)$ for some continuous $\lambda : I \to I$. In Section 4.5 the conditions on p_i and q_i, $i \in \{1, 2\}$ will be relaxed and the main results will be shown to hold when $p_i^2 + q_i^2 > 0$ and $q_i \geq 0$, $i \in \{1, 2\}$, only.

In the case of the single-compartment model for cell-division given in Chapter 1, Section 1.4, if the coefficients are independent of t, then the SSDs of the model satisfy an equation of the form (4.1.1), with $\lambda(x) = \alpha x$, $I = [0, \infty)$ and a zero-flux boundary condition at $x = 0$.

In Section 4.6 we examine the cumulative SSD of the single compartment model where all of the coefficients are constant and D is small. If $y(x)$ is the SSD in that case, the cumulative SSD $Y(x)$ is of the form

$$Y(x) = \int_0^\xi y(\xi)\, d\xi.$$

This all fits within the framework of the above general problem (4.1.1)-(4.1.3).

The proofs of existence of solutions to the above boundary value problem use the assumption of the existence of 'upper' and 'lower' solutions, which are defined in Section 4.3. For suitable f, the existence of a certain lower/upper solution pair $\phi(x)$, $\psi(x)$ guarantees the existence of a solution $y(x) \in C^2(I)$ such that $\phi(x) \leq y(x) \leq \psi(x)$ when $x \in I$. Graham-Eagle [26] used the upper and lower solutions in examining non-linear boundary value problems of the form

$$Lu = f(x, u, \nabla u, \Phi(u)), \qquad x \in \Omega,$$

$$Bu = 0, \qquad \partial\Omega,$$

with Ω a bounded domain in $\mathbb{R}^n$. L is a linear uniformly elliptic operator, B a linear boundary operator and Φ is a functional. The principal way in which this differs from the present problem is in the fact that the functional $\Phi(u)$ does not vary with x, and so for a solution u of the above problem with $\Phi(u) = C$, we find that u solves

$$Lu = f(x, u, \nabla u, C), \qquad x \in \Omega.$$

Against this it can be seen that in the present problem, the nonlocal component y^* can vary with x and therefore the problem is quite distinct.

Jiang and Wei [37] used upper and lower solutions for a periodic boundary value problem of the form

$$\begin{aligned} -y''(t) &= f(t, y(t), y(w(t))), \qquad t \in [0, T] \\ y(0) &= y(T), \\ y'(0) &= y'(T), \end{aligned}$$

with f and w continuous and $t - r \leq w(t) \leq t$ for some $r > 0$. It can be seen that the boundary conditions considered in [37] are different from those considered here and that the behaviour of w is more restricted than the behaviour of λ in this chapter.

The use of upper and lower solutions in a slightly different setting is found in [1], where they are used to prove an existence result for a time-scale boundary value problem.

The above papers all use slightly different, but analogous, definitions of upper/lower solutions.

Schrader [60] produced similar results to those proved here for local second-order ordinary differential equations with Dirichlet boundary conditions, establishing necessary and sufficient conditions for the existence of a solution between upper and lower solutions. Schmitt [59] proved an existence result on a finite interval for a (local) boundary value problem with similar boundary conditions to those specified here. Heidel [32] proved a similar result but with less restrictive conditions on f and relaxed conditions on p_i and q_i, $i \in \{0, 1\}$, such as shall be introduced in Section 4.5.

Here, a nonlocal term is introduced, with the proofs of the main results following closely the proofs of Schrader [60]. However, the addition of a nonlocal term demands certain changes. Primarily, Theorem 4.2.5, presented in Section 4.2, is used in this chapter in place of Theorem 3.2 from [31], used in the proofs of Schrader [60]. The condition (B) on f in Section 4.3 is imposed so that the assumptions of Theorem 4.2.5 are satisfied.

In Section 4.6, an application is shown of the theory developed in the preceding sections to a cell-growth model with a small dispersion parameter ε.

Finally, in Section 4.7, the theory developed in the previous sections is expanded to cover a wider variety of nonlocal terms in Equation (4.1.1).

4.2 An auxiliary theorem

In this section a theorem (Theorem 4.2.5) is presented which is needed in the subsequent proofs of existence. As the theorem is very specific, requiring many assumptions, it is suggested that the reader might wish to skip this section and come back at the point where it is required.

We begin with some definitions from [31]: Let $A \subset \mathbb{R}^d$ for some positive integer d and let F be a set of functions mapping $\mathbb{R}^d$ to $\mathbb{R}^{d'}$, for some $d' > 0$.

Definition 4.2.1. *The set of functions F is called* uniformly bounded *on A if there exists some $M > 0$ such that $|f(x)| \leq M$ for all $f \in F$ and $x \in A$.*

Definition 4.2.2. *The set of functions F is called* equicontinuous *on A if for any $\varepsilon > 0$ there exists a $\delta > 0$ such that $|f(x) - f(y)| \leq \varepsilon$ when $x, y \in A$ and $|x - y| \leq \delta$ for all $f \in F$.*

We now present, without proof, two theorems which are needed for the proof of the main result (Theorem 4.2.5) in this section. The first of these is Lemma 2.1 in [31]:

Lemma 4.2.3. *If a sequence of continuous functions on a compact set E is uniformly convergent on E, then it is uniformly bounded and equicontinuous.*

The following theorem is Theorem 2.3 in [31] and is commonly known as the Arzela-Ascoli Theorem [27].

Theorem 4.2.4. *On a compact set $E \subset \mathbb{R}^d$, let $f_1(y), f_2(y), \ldots$ be a sequence of functions which is uniformly bounded and equicontinuous on E. Then there exists a subsequence of functions which is uniformly convergent on E to a limit function $f(y)$.*

We now come to the main result of this section. This theorem is used here in place of Theorem 3.2 from [31] (used by Schrader [60]). It should be noted that Theorem 4.2.5 applies to a system of first order differential equations. Any n-th order differential equation can be expressed as a system of n first order differential equations. Thus the theorem applies to a more general class of problems than what we are examining. However, there are many assumptions made in the statement of the theorem, so it may only be useful inasmuch as it helps to prove the results in Section 4.3.

Let I be a compact interval and $|\cdot|$ be any norm on $\mathbb{R}^d$, $d > 0$. Let f and the sequence $f_1, f_2, \ldots$ be continuous functions defined on $(x, y, y^*) \in I \times \mathbb{R}^d \times \mathbb{R}^d = E$, mapping E into $\mathbb{R}^d$, such that the following assumptions hold:

(H_1) $f_n(x, y, y^*) \to f(x, y, y^*)$ uniformly on all compact subsets of E (so by Lemma 4.2.3, the functions f_n are uniformly bounded on all compact subsets of E).

(H_2) $f_n(x, y, y^*) = f_n(x, y, \gamma_n(x, y^*))$, where $\gamma_n : I \times \mathbb{R}^d \to \Gamma$; $\Gamma \subset \mathbb{R}^d$ compact, for all $n \geq 1$.

(H_3) Uniformly over all $x \in I$ and $y^* \in \Gamma$,

$$\sup_{n\geq 1}\{|f_n(x, y, y^*)|\} = O(|y|), \qquad \text{as } |y| \to \infty.$$

Then we obtain the following result:

Theorem 4.2.5. *Let $\Lambda(x)$ and the sequence $\lambda_1(x), \lambda_2(x), \ldots$ be continuous functions mapping I to $\mathbb{R}$ with $\lambda_n \to \Lambda$ uniformly on all compact intervals and $\lambda_n(A) \subset \Lambda(A)$ for all intervals $A \subset I$. Let there be given a sequence $(x_n, y_{n0}) \to (x_0, y_0) \in I \times \mathbb{R}^d$ as $n \to \infty$ and a sequence of functions $y_1(x), y_2(x), \ldots$ each defined on an interval containing I such that*

$$y_n'(x) = f_n(x, y_n(x), (y_n \circ \lambda_n)(x)), \qquad y(x_n) = y_{n0}$$

for all $x \in I$.

Then there exists a function $y(x)$ defined on I such that for any interval $A \subset I$ with $\Lambda(A) \subset I$, if A contains a neighbourhood of x_0, then

$$y'(x) = f(x, y(x), (y \circ \Lambda)(x)), \qquad y(x_0) = y_0, \tag{4.2.1}$$

for all $x \in A$. Moreover, there is a sequence of integers $n_1 < n_2 < \ldots$ such that

$$y_{n_k}(x) \to y(x)$$

uniformly on I as $k \to \infty$.

Proof. To prove this theorem it is first shown that for high enough $N > 0$, the sequence of functions $\{y_n(x)\}_{n=N}^{\infty}$ is uniformly bounded and equicontinuous in I. It therefore follows by the Arzela-Ascoli Theorem that there is a subsequence $y_{n_k} \to y$ uniformly in I as $k \to \infty$ for some limit function y. This limit function is then shown to be a solution of (4.2.1). In what follows $y_n^*(x)$ will be used to denote $(y_n \circ \lambda_n)(x)$.

There is a limit function: Pick any $b > 0$. By (H_1) and (H_2), the sequence f_n is uniformly bounded on $E_0 = \{(x, y, y^*) : |y - y_0| \leq b, x \in I\}$. Let M_0 be the least uniform upper bound on E_0. If $M_0 = 0$ then we are done, since for any $\varepsilon > 0$ we have $|y_{n0} - y_0| < b, \varepsilon$ for high enough n

and thus $y_n(x) = y_{n0}$ on the interval I with $|y_{n0} - y_0| < \varepsilon$. Therefore when $M_0 = 0$ the sequence $\{y_n\}_{n=1}^{\infty}$ tends uniformly on I as $n \to \infty$ to the constant function $y(x) = y_0$.

Now assume $M_0 > 0$. Let

$$\delta_n = |x_n - x_0|, \qquad \varepsilon_n = |y_{n0} - y_0|.$$

There exists an $N > 0$ such that for $n \geq N$ we have $\varepsilon_n < b/2$ and $\delta_n < a_0/2$. Define

$$a_0 = \frac{b}{2M_0}.$$

It is now claimed that all solutions $y_n(x)$, $n \geq N$ are uniformly bounded and equicontinuous on the interval $I_0 = [x_0 - a_0/2, x_0 + a_0/2] \cap I$ with $|y_n(x) - y_0| \leq b$ for all $x \in I_0$ and $n \geq 1$. For assume that for some y_n, $n \geq N$, we have $|y_n(x) - y_0| > b$ for some $x \in I_0$. We may express y_n as

$$y_n(x) = y_{n0} + \int_{x_n}^{x} f_n(s, y_n(s), y_n^*(s))\, ds,$$

and since $|y_{n0} - y_0| \leq b/2$ and the length of the interval is $\frac{b}{2M_0}$, we must have

$$|f_n(s, y_n(s), y_n^*(s))| > M_0$$

for some s between x_n and x. Now, since $y_n(x)$ is continuous we know by the Intermediate Value Theorem that there is some x in the interior of I_0 such that $|y_n(x) - y_0| = b$. Let x^* be the closest of these points to x_n (there must be a closest point or otherwise $y_n(x)$ is not continuous). Then by the above reasoning there is a point s between x_n and x^* such that $|f_n(s, y_n(s), y_n^*(s))| > M_0$. But this implies that $|y_n(s) - y_0| > b$, since otherwise f_n would be bounded by M_0. By the Intermediate Value Theorem this implies that there is a point x closer to x_n than x^* such that $|y_n(x) - y_0| = b$. This contradicts the definition of x^*, and thus the sequence $\{y_n\}_{n=N}^{\infty}$ is uniformly bounded on I_0. To see that we have equicontinuity, notice that since $|y_n(x) - y_0| \leq b$ for all $x \in I_0$ and $n \geq N$ we have $|f_n(x, y_n(x), y_n^*(x))| \leq M_0$ for all $x \in I_0$ and $n \geq N$. Therefore $|y_n(x) - y_n(x^*)| \leq M_0|x - x^*|$ for all $x, x^* \in I_0$ and $n \geq N$.

Choose any $\Delta b > 0$. Then let M_k, $k \geq 1$ be the least uniform upper bound for $|f_n(x, y, y^*)|$ on $E_k = \{(x, y, y^*) : |y - y_0| \leq b + k\Delta b, x \in I\}$ so that $M_0 \leq M_1 \leq \ldots$. Then on the interval

$$I_1 = [x_0 - a_1, x_0 + a_1] \cap I,$$

where

$$a_1 = \frac{a_0}{2} + \frac{\Delta b}{M_1},$$

the solutions y_n, $n \geq N$ are uniformly bounded and equicontinuous by a similar argument to the above. For from above we have $|y_n(x) - y_0| \leq b$ when $x \in I_0$ and so for $|y_n(x) - y_0|$ to be greater than $b + \Delta b$ on I_1 we must have $|f_n(x, y_n(x), y_n^*(x))| > M_1$ on $I_1 \setminus I_0$ and the same contradiction as above follows. Continuing this process with

$$a_k = a_{k-1} + \frac{\Delta b}{M_k},$$

we find that all solutions y_n, $n \geq N$ are uniformly bounded and equicontinuous on the interval $I_k = [t_0 - a_k, t_0 + a_k] \cap I$. Moreover, from (H_3) we know that $M_k = O(b + k\Delta b)$ as $k \to \infty$. Thus $a_k \to \infty$ as $k \to \infty$ and therefore, for all compact intervals in I, the sequence of functions $\{y_n(x)\}_{n=N}^{\infty}$ is uniformly bounded and equicontinuous. Specifically, the sequence of functions $\{y_n(x)\}_{n=N}^{\infty}$ is uniformly bounded and equicontinuous on I. Therefore, by the Arzela-Ascoli Theorem we may conclude that there is a subsequence of functions, which we now also denote by $\{y_n(x)\}_{n=0}^{\infty}$, converging uniformly to a limit function y. Note that $y(x)$ will also be bounded by the uniform bound of $\{y_n(x)\}_{n=0}^{\infty}$ on I.

The limit is a solution: Let $A \subset I$ be a compact interval containing an open neighbourhood of x_0, with $\Lambda(A) \subset I$. Since A is compact and Λ, λ_n are continuous, $\Lambda(A)$, $\lambda_n(A)$ are compact. Therefore the sequence of functions

$$y_n^*(x) = (y_n \circ \lambda_n)(x)$$

is uniformly bounded by the uniform bound of $\{y_n\}_{n=0}^{\infty}$ on $\Lambda(A)$. Moreover $y^*(x) = y \circ \Lambda(x)$ is bounded by the same bound.

Let B be the uniform bound of $|y_n(x) - y_0|$ on A and B^* be the uniform bound of $|y_n(x) - y_0|$ on $\Lambda(A)$. The functions f, f_n, $n \geq 1$ are continuous, and are thus uniformly continuous on any compact set. Hence, they are uniformly continuous on

$$U = \{(x, y, y^*) : |y - y_0| \leq B, |y^* - y_0| \leq B^*, x \in A\},$$

with $(x, y(x), y^*(x)), (x, y_n(x), y_n^*(x)) \in U$ for all $x \in A$ and $n \geq 1$. By Lemma 4.2.3 and (H_1) the functions f, $\{f_n\}$ are uniformly bounded on U. It will now be shown that $y(x)$ satisfies (4.2.1) on A.

For $x \in A$, consider

$$\mathcal{E}(x) = \left| y(x) - y_0 - \int_{x_0}^{x} f(s, y(s), (y \circ \Lambda)(s))\, ds \right|.$$

By the uniform continuity of f on U and the uniform convergence of y_n to y on A and $\Lambda(A)$, we find that for any $\varepsilon_1 > 0$ there exists an integer $N_1 > 0$ such that for all $n \geq N_1$ we have

$$\mathcal{E}(x) \leq \left| y(x) - y_0 - \int_{x_0}^{x} f(s, y_n(s), (y_n \circ \Lambda)(s))\, ds \right| + \varepsilon_1.$$

By the uniform convergence of λ_n to Λ on A, the equicontinuity of $\{y_n\}_{n=0}^{\infty}$ and the uniform continuity of f on U, we find that for any $\varepsilon_2 > 0$ there exists an integer $N_2 > N_1$ such that for all $n \geq N_2$ we have

$$\mathcal{E}(x) \leq \left| y(x) - y_0 - \int_{x_0}^{x} f(s, y_n(s), (y_n \circ \lambda_n)(s))\ ds \right| + \sum_{k=1}^{2} \varepsilon_k.$$

By the uniform convergence of f_n to f on U we find that for any $\varepsilon_3 > 0$ there exists some $N_3 > N_2$ such that for all $n \geq N_3$ we have

$$\mathcal{E}(x) \leq \left| y(x) - y_0 - \int_{x_0}^{x} f_n(s, y_n(s), (y_n \circ \lambda_n)(s))\ ds \right| + \sum_{k=1}^{3} \varepsilon_k.$$

By the convergence of (x_n, y_{n0}) to (x_0, y_0) and the uniform boundedness of all f_n on U, we find that for any $\varepsilon_4 > 0$ there exists an $N_4 > N_3$ such that for all $n \geq N_4$ we have $x_n \in A$ and

$$\begin{aligned} \mathcal{E}(x) &\leq \left| y(x) - y_{n0} - \int_{x_n}^{x} f_n(s, y_n(s), (y_n \circ \lambda_n)(s))\ ds \right| + \sum_{k=1}^{4} \varepsilon_k, \\ &= |y(x) - y_n(x)| + \sum_{k=1}^{4} \varepsilon_k. \end{aligned}$$

Finally, by the uniform convergence of y_n to y on A we find that for any $\varepsilon_5 > 0$ there exists an $N_5 > N_4$ such that for all $n \geq N_5$ we have

$$\mathcal{E}(x) = \left| y(x) - y_0 - \int_{x_0}^{x} f(s, y(s), (y \circ \Lambda)(s))\ ds \right| \leq \sum_{k=1}^{5} \varepsilon_k.$$

And since the ε_k, $k \in \{1, 2, 3, 4, 5\}$ are arbitrary it follows that $y(x)$ is a solution to (4.2.1) on A. This completes the proof of Theorem 4.2.5. □

4.3 Existence results for the general problem

In this section the three main theorems of this chapter: Theorems 4.3.4, 4.3.5 and 4.3.6, are presented. These theorems allow the inference of the existence of a solution of (4.1.1) between an upper/lower solution pair of functions. To begin with, some definitions are needed.

Definition 4.3.1. *Let I and J be intervals with $J \supset I$ and $\lambda : I \to J$ be a continuous function.*

1. *A C^2 function ϕ on the interval J is said to be a* lower λ-solution *of* (4.1.1) *on I if*

$$\phi''(x) \geq f(x, \phi(x), (\phi \circ \lambda)(x), \phi'(x))$$

for all $x \in I$.

2. *A C^2 function ψ on the interval J is said to be an* upper λ-solution *of* (4.1.1) *on I if*

$$\psi''(x) \leq f(x, \psi(x), (\psi \circ \lambda)(x), \psi'(x))$$

for all $x \in I$.

3. *A C^2 function y on the interval J is said to be a* λ-solution *of* (4.1.1) *on I if*

$$y''(x) = f(x, y(x), (y \circ \lambda)(x), y'(x))$$

for all $x \in I$.

Four assumptions used often in the statements of the following theorems are stated here for the sake of brevity in expressing the theorems:

(A_1) $\phi(x) \leq \psi(x)$ for all x in their domain of definition,

(A_2) $p_0\phi(a) - q_0\phi'(a) \leq A \leq p_0\psi(a) - q_0\psi'(a)$,

(A_3) $p_1\phi(b) + q_1\phi'(b) \leq B \leq p_1\psi(b) + q_1\psi'(b)$,

(A_4) $f(x, y, y^*, y')$ is non-increasing in y^* for $\phi^*(x) \leq y^* \leq \psi^*(x)$.

The condition (A_4) could be replaced by the more restrictive, but easier-to-check condition that $f(x, y, y^*, y')$ is non-increasing in y^* for any $(x, y, y') \in I \times \mathbb{R}^2$. Another condition we impose on f is

(B) $|f(x, y, y^*, y')| = O(|y'|)$ as $|y'| \to \infty$ uniformly on all compact subsets of

$$\{(x, y, y^*) : x \in I, \phi(x) \leq y \leq \psi(x), \phi^*(x) \leq y^* \leq \psi^*(x)\}.$$

Lemma 4.3.2. *Let $f(x, y, y^*, y')$ be continuous on $[a, b] \times \mathbb{R}^3$ and $\lambda : [a, b] \to [a, b]$ be a continuous function. Let there exist a constant $M > 0$ such that*

$$|f(x, y, y^*, y')| \leq M,$$

for all $(x, y, y^*, y') \in [a, b] \times \mathbb{R}^3$. Then the boundary value problem (4.1.1), (4.1.2) *and* (4.1.3) *has a λ-solution.*

The above lemma is essentially the same as Theorem 1 in [59] and has a similar proof. For completeness the proof, following [59] closely, is given below:

Proof. Let $G(x,\xi)$ be Green's function for the operator $\mathcal{L}y(x) = y''(x)$ along with the boundary conditions (4.1.2) and (4.1.3) when $A = B = 0$. We have

$$G(x,\xi) = C(\xi)x + D(\xi) + (x-\xi)H(x-\xi),$$

for some functions C and D of ξ. The boundary conditions then give the matrix equation

$$\begin{bmatrix} p_0a - q_0 & p_0 \\ p_1b + q_1 & p_1 \end{bmatrix} \begin{bmatrix} C \\ D \end{bmatrix} = \begin{bmatrix} 0 \\ p_1(\xi - b) - q_1 \end{bmatrix}. \tag{4.3.1}$$

Since p_0 and p_1 have are assumed to be positive, with q_0 and q_1 non-negative, the above matrix is invertible, and therefore Equation (4.3.1) has a solution for all $a \le \xi \le b$. Moreover, the coefficients C and D depend continuously on ξ. Therefore $G(x,\xi)$ exists, is continuous and bounded for $(x,\xi) \in [a,b]^2$ and also has its derivative $G_x(x,\xi)$ bounded for $(x,\xi) \in [a,b]^2$.

Let $\varphi(x)$ be a function such that $\varphi''(x) = 0$ for all $x \in [a,b]$ and let $\varphi(x)$ satisfy the boundary conditions (4.1.2) and (4.1.3). Such a solution exists, since we have

$$\varphi(x) = Cx + D,$$

for some constants C and D, with the boundary conditions (4.1.2) and (4.1.3) giving the matrix equation

$$\begin{bmatrix} p_0a - q_0 & p_0 \\ p_1b + q_1 & p_1 \end{bmatrix} \begin{bmatrix} C \\ D \end{bmatrix} = \begin{bmatrix} A \\ p_1(\xi - b) - q_1 + B \end{bmatrix}.$$

We have already found that the above matrix is invertible. Thus a suitable function $\varphi(x)$, as described above, exists.

Now, for any continuous function $h(x)$ we may write the solution of $y''(x) = h(x)$ satisfying (4.1.2) and (4.1.3) as

$$y(x) = \int_a^b G(x,\xi)h(\xi)\ d\xi + \varphi(x).$$

Let $\mathcal{B} = C^1[a,b]$ and for all $y \in \mathcal{B}$ define

$$||y|| = \sup_{x\in[a,b]} |y(x)| + \sup_{x\in[a,b]} |y'(x)|. \tag{4.3.2}$$

Then $\mathcal{B}$ is a Banach space. Define $T : \mathcal{B} \to \mathcal{B}$ as

$$Ty(x) = \int_a^b G(x,\xi)f(\xi, y(\xi), y^*(\xi), y'(\xi))\ d\xi + \varphi(x),$$

where $y \in \mathcal{B}$.

Letting

$$N = \sup_{[a,b]^2} |G(x,\xi)|(b-a),$$

$$N' = \sup_{[a,b]^2} |G_x(x,\xi)|(b-a),$$

$$L = \sup_{[a,b]} |\varphi(x)|,$$

$$L' = \sup_{[a,b]} |\varphi'(x)|,$$

it can be seen that

$$|Ty(x)| \leq NM + L, \qquad |(Ty)'(x)| \leq N'M + L'. \tag{4.3.3}$$

Therefore T maps the closed, bounded, and convex set

$$\mathcal{B}_1 = \{y \in \mathcal{B} : |y(x)| \leq NM + L, |y'(x)| \leq N'M + L'\}$$

into itself. Moreover T is a continuous mapping of $\mathcal{B}_1$ into itself. This is shown by first noting that $f(\xi, y, y^*, y')$ is continuous, and therefore is uniformly continuous on the compact set

$$(\xi, y, y^*, y') \in [a,b] \times [-NM - L, NM + L]^2 \times [-N'M - L', N'M' + L'].$$

Then given any $\varepsilon > 0$ it is possible to find some $\delta > 0$ such that whenever $y_1, y_2 \in \mathcal{B}_1$ and $||y_1 - y_2|| \leq \delta$ we have $||Ty_1 - Ty_2|| < \varepsilon$.

It is now claimed that $\overline{T\mathcal{B}_1}$ is compact, which is equivalent to $\overline{T\mathcal{B}_1}$ being sequentially compact. This will be proved using the Arzela-Ascoli Theorem.

Let $D\overline{T\mathcal{B}_1} = \{y' : y \in \overline{T\mathcal{B}_1}\}$ and consider $\overline{T\mathcal{B}_1}$ and $D\overline{T\mathcal{B}_1}$ as metric spaces under the sup-norm. It is obvious that the functions in $\overline{T\mathcal{B}_1}$ and $D\overline{T\mathcal{B}_1}$ are uniformly bounded (by Equation (4.3.3)). We now need to show equicontinuity, so that an application of the Arzela-Ascoli Theorem will show sequential compactness of $\overline{T\mathcal{B}_1}$ in the norm (4.3.2).

Note that since $G(x,\xi)$ is continuous, it is uniformly continuous on $[a,b]^2$. Moreover $\varphi(x)$ is uniformly continuous on $[a,b]$. Thus we have that for any $\varepsilon > 0$ there exists a $\delta > 0$ such that when $|x - x_0| < \delta$ we have

$$|y(x) - y(x_0)| \leq \int_a^b |G(x,\xi) - G(x_0,\xi)|M \; d\xi + |\varphi(x) - \varphi(x_0)| < \varepsilon,$$

for any $y \in T\mathcal{B}_1$.

Now, recall that $G_x(x,\xi)$ is bounded. Thus, for $a \leq x_0 < x \leq b$ we have

$$\begin{aligned} |y'(x) - y'(x_0)| &\leq \int_a^b |G_x(x,\xi) - G_x(x_0,\xi)|M \ d\xi + |\varphi'(x) - \varphi'(x_0)|, \qquad (4.3.4) \\ &\leq \int_a^{x_0} |G_x(x,\xi) - G_x(x_0,\xi)|M \ d\xi + \int_{x_0}^{x} \frac{2N'M}{b-a} \ d\xi \\ &\quad + \int_x^b |G_x(x,\xi) - G_x(x_0,\xi)|M \ d\xi. \end{aligned}$$

The term $|\varphi'(x) - \varphi'(x_0)|$ disappears because $\varphi'(x)$ is constant. Note that $G_x(x,\xi)$ is uniformly continuous in the regions $b \geq x > \xi \geq a$ and $a \leq x < \xi \leq b$. Thus, from (4.3.4), we find that for any $\varepsilon > 0$ there exists a $\delta > 0$ such that

$$|y'(x) - y'(x_0)| < \varepsilon$$

for all $|x - x_0| < \delta$ and $y \in T\mathcal{B}_1$.

The same holds for any $y \in \overline{T\mathcal{B}_1}$, since for any $\varepsilon > 0$ we may choose some $y_0 \in T\mathcal{B}_1$ such that $||y - y_0|| < \varepsilon/4$, and a $\delta > 0$ such that

$$|y_0(x) - y_0(x_0)| < \varepsilon/2, \qquad |y_0'(x) - y_0'(x_0)| < \varepsilon/2,$$

whenever $|x - x_0| < \delta$. Thus we find that

$$|y(x) - y(x_0)| < \varepsilon, \qquad |y'(x) - y'(x_0)| < \varepsilon,$$

whenever $|x - x_0| < \delta$. We have now found that $\overline{T\mathcal{B}_1}$ and $D\overline{T\mathcal{B}_1}$ are equicontinuous.

Now, by the Arzela-Ascoli Theorem, we find that for any sequence $\{y_k\}_{k=1}^{\infty} \in \overline{T\mathcal{B}_1}$ we may choose a subsequence such that the terms converge in the norm (4.3.2) to a limit in $\overline{T\mathcal{B}_1}$. This is the definition of sequential compactness and therefore we find that $\overline{T\mathcal{B}_1}$ is compact.

We now apply the Schauder Fixed Point Theorem (see Theorem 2.A, Section 2.6 of [71]) to show that T has a fixed point in $\mathcal{B}_1$. On the other hand fixed points of T are solutions of the problem (4.1.1)-(4.1.3). This completes the proof. $\square$

The next lemma, where $f(x, y, y^*, y')$ is assumed to be bounded, is used many times in the proofs of the theorems which follow.

Lemma 4.3.3. *Let the I and J be intervals; $I = [a,b]$, $J \supset I$; $\eta : I \to I$ and $\lambda : I \to J$ be continuous functions and $f(x, y, y^*, y')$ be defined as in Lemma 4.3.2. Let ϕ, ψ be lower/upper λ-solutions of* (4.1.1) *on I respectively, such that (A_1)-(A_4) hold. Define*

$$G(x, y, y^*, y') = \begin{cases} f(x, y, \psi^*(x), y'), & \psi^*(x) < y^*, \\ f(x, y, y^*, y'), & \phi^*(x) \leq y^* \leq \psi^*(x), \\ f(x, y, \phi^*(x), y'), & y^* < \phi^*(x), \end{cases}$$

where $\phi^*(x) = (\phi \circ \lambda)(x)$ *and* $\psi^*(x) = (\psi \circ \lambda)(x)$.

There exists an η*-solution* y *on the interval* I *to the boundary value problem*

$$y'' = G(x, y, y^*, y'), \tag{4.3.5}$$

with boundary conditions (4.1.2) *and* (4.1.3), *such that* $\phi(x) \le y(x) \le \psi(x)$ *for all* $x \in I$. *Furthermore if* $\eta(x) = \lambda(x)$ *for all* $x \in I$ *then* y *is a* λ*-solution to* (4.1.1) *on* I.

Proof. Let

$$F(x, y, y^*, y') = \begin{cases} G(x, \psi(x), y^*, y') + \frac{y-\psi(x)}{1+y^2}, & \psi(x) < y, \\ G(x, y, y^*, y'), & \phi(x) \le y \le \psi(x), \\ G(x, \phi(x), y^*, y') + \frac{y-\phi(x)}{1+y^2}, & y < \phi(x), \end{cases} \tag{4.3.6}$$

Since f is bounded, F is also bounded. Moreover, F is continuous. Thus, by Lemma 4.3.2 an η-solution to

$$y'' = F(x, y, y^*, y'),$$

and the boundary conditions (4.1.2), (4.1.3) exists. Call this solution $y(x)$. It will now be shown that $\phi(x) \le y(x) \le \psi(x)$ for all $x \in I$.

Assume that $y(x) > \psi(x)$ for some $x \in I$. Then there exists an interval $[c, d] \subset I$ such that:

- $y(x) > \psi(x)$ for all $x \in (c, d)$,
- Either $y(c) = \psi(c)$ or we have $c = a$ and $y(a) > \psi(a)$,
- Either $y(d) = \psi(d)$ or we have $d = b$ and $y(b) > \psi(b)$.

Take any such interval $[c, d]$. If $y(c) = \psi(c)$ then $y'(c_0) > \psi'(c_0)$ for some $c_0 \in [c, c+\delta]$, $0 < \delta < (d-c)/2$. If $c = a$ and $y(a) > \psi(a)$ then we must have $q_0 > 0$ and $y'(a) > \psi'(a)$. In either case we have $y'(c_0) > \psi'(c_0)$ for some $c_0 \in [c, c+\delta]$. Similarly $y'(d_0) < \psi'(d_0)$ for some $d_0 \in [d, d-\varepsilon]$, $0 < \varepsilon < (d-c)/2$. Therefore there must exist a local maximum point $z_0 \in (c_0, d_0)$ of $y - \psi$ such that $y'(z_0) = \psi'(z_0)$ and $(y-\psi)''(z_0) \le 0$. However, from (4.3.6) we find that

$$\begin{aligned} (y'' - \psi'')(z_0) &= G(z_0, \psi(z_0), (y \circ \eta)(z_0), \psi'(z_0)) + \frac{y(z_0) - \psi(z_0)}{1 + y(z_0)^2} \\ &\quad - f(z_0, \psi(z_0), \psi^*(z_0), \psi'(z_0)). \end{aligned}$$

By the definition of G and assumption (A_4), we find from the above expression that $(y''-\psi'')(z_0) > 0$. This is a contradiction and thus $y(x) \le \psi(x)$ for all $x \in I$. The proof that $\phi(x) \le y(x)$ for all $x \in I$ is similar. Therefore, since $\phi(x) \le y(x) \le \psi(x)$ for $x \in I$, we see that y is an η-solution to (4.3.5) and the boundary conditions (4.1.2) and (4.1.3).

Finally, if $\lambda(x) = \eta(x)$ for all $x \in I$ then, since $\phi(x) \le y(x) \le \psi(x)$ for all $x \in I$ we also have $\phi^*(x) \le y^*(x) \le \psi^*(x)$ for all $x \in I$. Thus, from the definition of F and G one can see that y is a solution of (4.1.1) with boundary conditions (4.1.2) and (4.1.3). This completes the proof. $\square$

We now come to the first main result of this chapter. It extends the above result to cope with unbounded functions f, but only if assumption (B) is satisfied. Like the two other results that follow, the proof of the next theorem follows the analogous proof of Schrader [60] closely.

Theorem 4.3.4. *Let $I = [a,b]$ and let $f(x,y,y^*,y')$ be continuous on $I \times \mathbb{R}^3$. Let $\lambda : I \to I$ be continuous and let $\phi(x)$ and $\psi(x)$ be lower and upper λ-solutions to* (4.1.1) *respectively. Assume that (A_1)-(A_4) and (B) hold. Then there exists a λ-solution y to* (4.1.1) *with boundary conditions* (4.1.2) *and* (4.1.3) *such that $\phi(x) \le y(x) \le \psi(x)$ for all $x \in I$.*

Proof. Let G be defined as in Lemma 4.3.3. Let $N > 1$ be an integer such that $|\phi'(x)| \le N$ and $|\psi'(x)| \le N$ on I. Then define the function F_N on $I \times \mathbb{R}^3$ by

$$F_N(x,y,y^*,y') = \begin{cases} F_1(x,y,y^*,N), & y' > N, \\ F_1(x,y,y^*,y'), & |y'| \le N, \\ F_1(x,y,y^*,-N), & y' < -N, \end{cases}$$

where

$$F_1(x,y,y^*,y') = \begin{cases} G(x,\psi(x),y^*,y'), & y > \psi(x), \\ G(x,y,y^*,y'), & \phi(x) \le y \le \psi(x), \\ G(x,\phi(x),y^*,y'), & y < \phi(x). \end{cases}$$

Note that by the continuity of f and the construction of F_N we know that $F_N(x,y,y^*,y')$ is bounded for $(x,y,y^*,y') \in I \times \mathbb{R}^3$. Therefore, by Lemma 4.3.3 and the fact that ϕ, ψ are lower and upper λ-solutions respectively of

$$y'' = F_N(x,y,y^*,y'), \tag{4.3.7}$$

there exists a λ-solution $y_N(x)$ to (4.3.7) satisfying the boundary conditions (4.1.2) and (4.1.3) such that $\phi(x) \le y_N(x) \le \psi(x)$ for all $x \in I$.

The functions F_N converge uniformly to F_1 on all compact sets $I \times \mathbb{R}^3$. Moreover, for each F_N,

$$F_N(x,y,y^*,y') = F_N(x,y,\gamma(x,y^*),y'),$$

where

$$\gamma(x, y^*) = \begin{cases} \psi^*(x), & y^* > \psi^*(x), \\ y^*, & \phi^*(x) \le y^* \le \psi^*(x), \\ \phi^*(x), & y^* < \phi^*(x). \end{cases}$$

Finally, from (B) and the construction of F_N, we know that uniformly over $\{(x, y, y^*) : x \in I, y \in \mathbb{R}, y^* \in \psi(x, \mathbb{R})\}$

$$\sup_N |F_N(x, y, y^*, y')| = O(|y'|)$$

as $|y'| \to \infty$; and therefore that uniformly over $\{(x, y^*) : x \in I, y^* \in \gamma(I, \mathbb{R})\}$

$$\sup_N |F_N(x, y, y^*, y')| = O(||(y, y')||_2)$$

as $||(y, y')||_2 \to \infty$, where $|| \cdot ||_2$ denotes the Euclidean 2-norm. Thus, the sequence of natural extensions of F_N to systems of first order differential equations for (y, y') satisfies (H_1)-(H_3) using the norm $|| \cdot ||_2$in Theorem 4.2.5. That is, the sequence of functions $\overline{F}_N$ satisfies (H_1)-(H_3), where

$$\overline{F}_N(x, y, y', y^*, y^{*'}) = (y', F_N(x, y, y^*, y'))$$

The corresponding (constant) sequence of nonlocal functions $\lambda, \lambda, \ldots$, with uniform limit λ, also satisfies the conditions required in Theorem 4.2.5.

We now construct a sequence of points $(x_N, y_N(x_N), y'_N(x_N))$ in $I \times \mathbb{R}^2$ as follows: Choose x_N by the mean value theorem so that $y_N(b) - y_N(a) = (b - a)y'_N(x_N)$. It then follows that

$$\begin{aligned} |y'_N(x_N)| &= \frac{|y_N(b) - y_N(a)|}{b - a} \\ &\le \max\{|\psi(a) - \psi(b)|, |\psi(a) - \phi(b)|, |\phi(a) - \psi(b)|, |\phi(a) - \phi(b)|\}/(b - a). \end{aligned} \tag{4.3.8}$$

Since $\{x_N\}$, $\{y_N(x_N)\}$ and $\{y'_N(x_N)\}$ are each bounded sequences, we may make consecutive choices of convergent subsequences; denoting the resulting subsequence in the same way as the original sequence. So that we now have

$$(x_N, y_N(x_N), y'_N(x_N)) \to (x_0, y_0, y'_0)$$

as $N \to \infty$ for some limit (x_0, y_0, y'_0).

It now follows from Theorem 4.2.5 that there is a λ-solution y of the initial value problem

$$y'' = F_1(x, y, y^*, y'),$$
$$y(x_0) = y_0, \qquad y'(x_0) = y'_0$$

on I with $\phi(x) \leq y(x) \leq \psi(x)$. Moreover, since the convergence in the proof of Theorem 4.2.5 is in (y, y'), we see that $(y(a), y'(a))$ is the limit of a convergent subsequence of $(y_N(a), y'_N(a))$ and thus y satisfies the boundary condition (4.1.2). Similarly y satisfies the boundary condition (4.1.3). Since y is a λ-solution and ϕ and ψ are lower and upper λ-solutions, we see that $\phi^*(x) \leq y^*(x) \leq \psi^*(x)$ for all $x \in I$ and thus y is a λ-solution of (4.1.1). $\square$

Theorem 4.3.5. *Let $I = [a, \infty)$ and let $f(x, y, y^*, y')$ be continuous in $I \times \mathbb{R}^3$. Let $\Lambda : I \to I$ be continuous and let ϕ and ψ be lower and upper Λ-solutions to* (4.1.1) *respectively. Assume (A_1),(A_2),(A_4) and (B) hold. Then there exists a Λ-solution $y(x)$ to* (4.1.1) *with boundary condition* (4.1.2) *such that $\phi(x) \leq y(x) \leq \psi(x)$ for all $x \in I$.*

Proof. Let $a_n = a + n$ for all $n \geq 1$ and form the sequence of intervals $I_n = [a, a_n]$, $n = 1, 2, \ldots$. Form the corresponding sequence of intervals $J_n = [a, b_n]$, $n = 1, 2, \ldots$, where

$$b_n = \max\left\{\max_{x \in I_n} \Lambda(x), a_n\right\}.$$

We then have $\Lambda(I_n) \subset J_n$ for all $n \geq 1$. Finally, form the sequence of values π_n, $n = 1, 2, \ldots$, such that $\phi(b_n) \leq \pi_n \leq \psi(b_n)$ for all $n \geq 1$. Define $\lambda_n : I \to J_n$, $n \geq 1$, as

$$\lambda_n(x) = \begin{cases} b_n, & \Lambda(x) > b_n, \\ \Lambda(x), & \Lambda(x) \leq b_n. \end{cases}$$

For the interval J_n, let N, F_N and F_1 be defined as in the proof for Theorem 4.3.4 (with $\phi^*(x) = (\phi \circ \Lambda)(x)$ and $\psi^*(x) = (\psi \circ \Lambda)(x)$). From Lemma 4.3.3 it follows that the boundary value problem

$$y'' = F_N(x, y, y^*, y'),$$
$$p_0 y(a) - q_0 y'(a) = A, \qquad y(b_n) = \pi_n,$$

has a λ_n-solution y_N on J_n with $\phi(x) \leq y_N(x) \leq \psi(x)$ for all $x \in J_n$. Using the same reasoning as in Theorem 4.3.4, we see that the functions F_N satisfy (H_1)-(H_3), the conditions necessary for the use Theorem 4.2.5 (when extended to a system of differential equations). Pick x_N so that $y_N(b_n) - y_N(a) = (b_n - a)y'_N(x_N)$. It then follows (as in Theorem 4.3.4) that the sequences $\{x_N\}$, $\{y_N(x_N)\}$ and $\{y'_N(x_N)\}$ are bounded and so by consecutively picking convergent subsequences and using the similar reasoning to the proof of Theorem 4.3.4 we conclude that there is a λ_n-solution y_n of

$$y'' = F_1(x, y, y^*, y'),$$
$$p_0 y(a) - q_0 y'(a) = A, \qquad y(b_n) = \pi_n,$$

such that $\phi(x) \le y_n(x) \le \psi(x)$ for all $x \in J_n$. Moreover, since $\lambda_n = \Lambda$ on I_n we find that y_n is a Λ-solution on the interval I_n.

Now, for any interval J_n consider the constant sequence of functions $F_1, F_1, \ldots$. This is uniformly convergent on all compact sets in $I \times \mathbb{R}^3$ to F_1. Moreover, on the interval J_n,

$$F_1(x, y, y^*, y') = F_1(x, y, \gamma(x, y^*), y'),$$

where $\gamma(x, y^*)$ is defined as in Theorem 4.3.4 (but with $\phi^* = \phi \circ \Lambda$ and $\psi^* = \psi \circ \Lambda$). Furthermore, from (B) and the construction of F_1, we know that

$$|F_1(x, y, y^*, y')| = O(||(y, y')||_2)$$

as $||(y, y')||_2 \to \infty$ uniformly over $\{(x, y^*) : x \in J_n, y^* \in \gamma(J_n, \mathbb{R})\}$. Finally, the sequence of functions λ_n tends to Λ uniformly on all compact intervals in J_n with $\lambda_n(A) \subset \Lambda(A)$ for all intervals $A \subset J_n$. Thus (H_1)-(H_3) are satisfied (when we extend F_1 to a system of first order differential equations), along with the assumptions on the sequence λ_n in Theorem 4.2.5 on the interval J_n. We shall now find a suitable sequence of solutions of initial-value problems converging uniformly on all compact subsets of I.

All solutions y_m for $m \ge n + 1$ are defined on an interval containing $J_n = [a, b_n]$ and by the mean value theorem we may pick $x_{nm} \in [a, b_n]$ such that

$$y_m(b_n) - y_m(a) = (b_n - a)y_m'(x_{nm}).$$

Thus the sequence $y_m'(x_{nm})$, $m = n+1, n+2, \ldots$ is bounded in a similar way to (4.3.8) from Theorem 4.3.4.

For $n = 1$ we may consecutively pick subsequences as m varies of

$$\{x_{nm}\}, \qquad \{y_m(x_{nm})\}, \qquad \{y_m'(x_{nm})\}$$

which converge. It then follows from Theorem 4.2.5 that there is a subsequence of $\{y_m\}$, denoted by S_1 which converges on the interval J_1 to a Λ-solution of (4.1.1) on the interval I_1 satisfying the boundary condition (4.1.2). If we repeat this process for each interval J_n, and at each step take subsequences of the appropriate previous subsequences, we may form the sequence of subsequences

$$S_1 \supset S_2 \supset S_3 \supset \ldots,$$

with the subsequence S_n converging on J_n to Λ-solution of (4.1.1) on the interval I_n satisfying the boundary condition (4.1.2). Taking the diagonal sequence S_d from $S_1, S_2, \ldots$, we then have a subsequence of $\{y_n\}_{n=1}^{\infty}$ which converges to a Λ-solution y of (4.1.1) such that $\phi(x) \leq y(x) \leq \psi(x)$ on all compact intervals in $[a, \infty)$. Furthermore, as in Theorem 4.3.4, the limit function y satisfies the boundary condition (4.1.2). $\square$

Theorem 4.3.6. *Let $I = (-\infty, \infty)$ and let $f(x, y, y^*, y')$ be continuous in $I \times \mathbb{R}^3$. Let $\Lambda : I \to I$ be continuous and let ϕ and ψ be lower and upper Λ-solutions to* (4.1.1) *respectively. Assume (A_1),(A_4) and (B) hold. Then there exists a Λ-solution $y(x)$ to* (4.1.1) *such that $\phi(x) \leq y(x) \leq \psi(x)$ for all $x \in I$.*

Proof. Let $a_n = -n$, $b_n = n$ for all $n \geq 1$ and form the sequence of intervals $I_n = [a_n, b_n]$, $n = 1, 2, \ldots$. Form the corresponding sequence of intervals $J_n = [c_n, d_n]$, $n = 1, 2, \ldots$, where

$$c_n = \min\left\{\min_{x \in I_n} \Lambda(x), a_n\right\}, \qquad d_n = \max\left\{\max_{x \in I_n} \Lambda(x), b_n\right\}.$$

We then have $\Lambda(I_n) \subset J_n$ for all $n \geq 1$. Finally, form the sequences of values θ_n, π_n, $n = 1, 2, \ldots$, such that $\phi(c_n) \leq \theta_n \leq \psi(c_n)$ and $\phi(d_n) \leq \pi_n \leq \psi(d_n)$ for all $n \geq 1$. Define $\lambda_n : I \to J_n$, $n \geq 1$, as

$$\lambda_n(x) = \begin{cases} d_n, & \Lambda(x) > d_n, \\ \Lambda(x), & c_n \leq \Lambda(x) \leq d_n, \\ c_n, & \Lambda(x) < c_n. \end{cases}$$

The proof may now be completed in a similar manner to the proof for Theorem 4.3.5. $\square$

4.4 More general upper and lower solutions

Similar results will hold if we allow the upper and lower solutions ϕ and ψ to have isolated points where they are not C^2.

Definition 4.4.1. *Let I and J be intervals with $J \supset I$ and $\lambda : I \to J$ be a continuous function.*

1. *Let ϕ be a continuous, piecewise C^2 function on an interval J with finitely many points of discontinuity (of the derivative) $x_0 < x_1 < \ldots < x_m$ in the interior of J such that for all $0 \leq n \leq m$ we have*

$$\phi'(x_n^-) \leq \phi'(x_n^+).$$

   ϕ is said to be a generalised lower λ-solution *of* (4.1.1) *on I if*

$$\phi''(x) \geq f(x, \phi(x), (\phi \circ \lambda)(x), \phi'(x))$$

   for all $x \in [x_n, x_{n+1}] \cap I$, $0 \leq n \leq m-1$, and $x \in [x_m, \infty) \cap I$, where the derivatives the end-points of each interval are taken from above and below where appropriate.

2. *Let ψ be a continuous, piecewise C^2 function on an interval J with finitely many points of discontinuity $x_0 < x_1 < \ldots < x_m$ in the interior of J such that for all $0 \le n \le m$ we have*

$$\psi'(x_n^-) \ge \psi'(x_n^+).$$

ψ is said to be a generalised upper λ-solution *of* (4.1.1) *on I if*

$$\psi''(x) \le f(x, \psi(x), (\psi \circ \lambda)(x), \psi'(x))$$

for all $x \in [x_n, x_{n+1}] \cap I$, $0 \le n \le m-1$, and $x \in [x_m, \infty) \cap I$, where the derivatives at the end-points of each interval are taken from above and below where appropriate.

In both of the above cases it is assumed that there are only finitely many points of discontinuity in any finite interval in I.

Using this definition we may now re-prove Lemma 4.2.3 using generalised upper and lower λ-solutions instead of regular upper and lower λ-solutions. The other results in this chapter are then seen to hold when ϕ, ψ are generalised, rather than regular, upper and lower λ-solutions.

Lemma 4.4.2. *Let the I and J be intervals; $I = [a, b]$, $J \supset I$; $\eta : I \to I$ and $\lambda : I \to J$ be continuous functions and $f(x, y, y^*, y')$ be defined as in Lemma 4.3.2. Let ϕ, ψ be generalised lower/upper λ-solutions of* (4.1.1) *on I respectively, such that (A_1)-(A_4) hold. Define G as in Lemma 4.3.3. Then the conclusion of Lemma 4.3.3 holds.*

Proof. Define F as in Lemma 4.3.3. The existence of a η-solution, $y(x)$, to

$$y'' = F(x, y, y^*, y')$$

with the boundary conditions (4.1.2) and (4.1.3) follows in the same way as in Lemma 4.3.3. Assume that $y(x) > \psi(x)$ for some $x \in I$. The existence of an interval $[c, d]$ as described in Lemma 4.3.3 follows in much the same way as before, along with the points $c_0 < d_0 \in [c, d]$ such that c_0 and d_0 are not points of discontinuity of ψ and $y'(c_0) > \psi'(c_0)$, $y'(d_0) < \psi'(d_0)$.

Let $c_0 = x_0 < x_1 < \ldots < x_N = d_0$ be the points of discontinuity of ψ in (c_0, d_0) along with the endpoints c_0 and d_0. Define the interval $I_n = [x_n, x_{n+1}]$, $0 \le n \le N-1$. Let k be the greatest integer such that $y'(x) > \psi'(x)$ for all $x \in I_n$ when $n < k$. Then

$$y'(x_k) > \psi'(x_k^-) \ge \psi'(x_k^+).$$

Therefore on I_k we have $y'(x_k) > \psi'(x_k)$ and $y'(z_0) = \psi'(z_0)$ for some $x_k < z_0 \in I_k$ such that $y'(x) > \psi'(x)$ for all $x \in (x_k, z_0)$. We can conclude from this that $(y'' - \psi'')(z_0^-) \le 0$. But, from

(4.3.6) we find, as in Lemma 4.3.3, that $(y'' - \psi'')(z_0^-) > 0$. This is a contradiction and thus $y(x) \leq \psi(x)$ for all $x \in I$. Similarly $\phi(x) \leq y(x)$ for all $x \in I$. The remainder of the proof is the same as in Lemma 4.3.3. □

Replacing the use of Lemma 4.3.3 with Lemma 4.4.2 in Theorems 4.3.4, 4.3.5 and 4.3.6 allows the use of generalised lower and upper λ-solutions in place of regular lower and upper λ-solutions. In the following sections the word 'generalised' will be dropped, so that both regular and generalised upper/lower solutions will be referred to simply as upper/lower solutions.

4.5 Relaxation of the conditions on p_i and q_i, $i \in \{0, 1\}$

In this section it is proved that the requirements on the coefficients p_i and q_i, $i \in \{0, 1\}$ can be relaxed, so that the only requirement apart from $p_i^2 + q_i^2 > 0$ is that $q_i \geq 0$ for $i \in \{0, 1\}$. The proof of this is taken from the beginning of the proof of Heidel [32]. The cases where $I = [a, b]$ and $I = [a, \infty)$ are the only cases considered in this section. There are no boundary conditions when $I = (-\infty, \infty)$, so this section is irrelevant to that case.

Lemma 4.5.1. *The conditions*

$$p_i^2 + q_i^2 > 0,$$
$$q_i \geq 0,$$

for $i \in \{0, 1\}$ are sufficient for Theorem 4.3.4 to hold.

Proof. Assume $I = [a, b]$. Without loss of generality we may assume $a < 0$ and $b > 0$. If this were not the case then let $\xi = x - \frac{a+b}{2}$ and let ϕ, ψ, f, λ be functions satisfying the assumptions of Theorem 4.3.4. Define $u(\xi) = y(x)$ and on the new interval $J = [(a - b)/2, (b - a)/2]$ define $\eta : J \to J$ such that

$$\eta(\xi) = \lambda(x) - \frac{a + b}{2}.$$

Then (4.1.1) becomes

$$u''(\xi) = f\left(\xi + \frac{a + b}{2}, u(\xi), u^*(\xi), u'(\xi)\right) = g(\xi, u, u^*, u') \tag{4.5.1}$$

for all $\xi \in J$. Note that if y is a λ-solution to (4.1.1) on I then u is an η-solution to (4.5.1) on J and vice-versa. Define $\overline{\phi}(\xi) = \phi(x)$ and $\overline{\psi}(\xi) = \psi(x)$. Then $\overline{\phi}$ is a lower η-solution and $\overline{\psi}$ is an upper η-solution of (4.5.1) on J. Moreover, assumptions (A_1)-(A_4) and (B) are satisfied for $\overline{\psi}$, $\overline{\phi}$ and g (where (A_2) and (A_3) are satisfied at the end-points of the interval J). Thus, if u is an η-solution of (4.5.1) satisfying the appropriate boundary conditions with $\overline{\phi}(\xi) \leq u(\xi) \leq \overline{\psi}(\xi)$ when $x \in J$, then by reversing the translation we find that y is a λ-solution of (4.1.1) satisfying the boundary conditions (4.1.2) and (4.1.3) with $\phi(x) \leq y(x) \leq \psi(x)$ for all $x \in I$.

We now assume that $a < 0$ and $b > 0$. Let

$$\begin{aligned} u &= ye^{\frac{Lx^2}{2}}, \\ \overline{\phi} &= \phi e^{\frac{Lx^2}{2}}, \\ \overline{\psi} &= \psi e^{\frac{Lx^2}{2}}, \end{aligned}$$

for some constant L which shall be specified later. The boundary value problem (4.1.1), (4.1.2) and (4.1.3) then becomes

$$\begin{aligned} u'' &= e^{\frac{Lx^2}{2}} f(x, y, y^*, y') + 2xLu' - (x^2L^2 - L)u, \qquad (4.5.2) \\ &= g(x, u, u^*, u'), \\ r_0u(a) - q_0u'(a) &= Ae^{\frac{La^2}{2}}, \qquad (4.5.3) \\ r_1u(b) + q_1u'(b) &= Be^{\frac{Lb^2}{2}}, \qquad (4.5.4) \end{aligned}$$

with

$$r_0 = p_0 + aLq_0, \qquad r_1 = p_1 - bLq_1.$$

Note that the functions $\overline{\psi}$ and $\overline{\phi}$ are upper and lower λ-solutions respectively to the boundary value problem (4.5.2)-(4.5.4). Moreover $\overline{\psi}$, $\overline{\phi}$, g and λ satisfy (A_1)-(A_4) and (B).

If $q_0, q_1 > 0$ then choose $L < 0$ such that $r_0, r_1 > 0$. If $q_0 = 0$ (resp. $q_1 = 0$) then choose $L < 0$ such that $r_1 > 0$ (resp. $r_0 > 0$). If both $q_0, q_1 = 0$ then let $L = 0$. Assume for now that if $q_i = 0$, $i \in \{0, 1\}$, then $p_i > 0$. The new boundary value problem (4.5.2)-(4.5.4) along with the functions ψ, ϕ, g and λ satisfies the assumptions of Theorem 4.3.4 and thus there is a λ-solution u such that $\overline{\phi}(x) \leq u(x) \leq \overline{\psi}(x)$ for all $x \in I$. Applying the reverse transform to u gives a λ-solution y to (4.1.1) such that $\phi(x) \leq y(x) \leq \psi(x)$ for all $x \in I$.

In the cases where $p_0 < 0$ and $q_0 = 0$, or $p_1 < 0$ and $q_1 = 0$, or both, Lemma 4.3.2 is seen to hold when we multiply the boundary conditions (4.1.2), or (4.1.3), or both by -1, so that a λ-solution exists to (4.1.1)-(4.1.3) on $[a, b]$.

In the case that $p_0 < 0$ and $q_0 = 0$, for assumptions (A_1) and (A_2) to hold at the same time we must have the generalised lower and upper λ-solutions ϕ and ψ satisfying the boundary condition (4.1.2). Similarly if $p_1 < 0$ and $q_1 = 0$, for the assumptions (A_1) and (A_3) to hold at the same time we must have ϕ and ψ satisfying the boundary condition (4.1.3). Lemma 4.4.2 then holds in either of these cases. Therefore Theorem 4.3.4 also holds. $\square$

Corollary 4.5.2. *The conditions*

$$p_0^2 + q_0^2 > 0,$$
$$q_0 \geq 0,$$

for $i \in \{0, 1\}$ are sufficient for Theorem 4.3.5 to hold.

Proof. As before, we may assume without loss of generality that $a < 0$, for if $a > 0$ we may apply the shift transform $\xi = x - 2a$. To complete the proof proceed similarly to the proof of Lemma 4.5.1. $\square$

4.6 Application of the theory in a cell-growth setting

We desire an estimate of the solution of

$$\varepsilon y''(x) = gy'(x) - \alpha by(\alpha x) + \alpha by(x), \tag{4.6.1}$$

for $\varepsilon > 0$ small, where $b, g > 0$ and $\alpha > 1$ are constants. Equation (4.6.1) is supplemented by the boundary conditions

$$y(0) = 0, \tag{4.6.2}$$
$$\lim_{x \to \infty} y(x) = 1. \tag{4.6.3}$$

In this problem we have $\lambda(x) = \alpha x$ for all $x \geq 0$.

We can regard the solution of (4.6.1) satisfying the boundary conditions (4.6.2) and (4.6.3) as the shape of a *cumulative* size-distribution of cells undergoing growth and division at constant rates for all cell sizes. The solution of the ODE is the cumulative distribution corresponding to a SSD of the following model for the evolution of the size-distribution of a population of cells:

$$n_t(x,t) = \varepsilon n_{xx}(x,t) - gn_x(x,t) + \alpha^2 bn(\alpha x, t) - (b + \mu)n(x,t). \tag{4.6.4}$$

This is the single-compartment model from Section 1.4 with constant coefficients, and the dispersion coefficient D replaced by ε to indicate that it is a small parameter in the present situation. Equation (4.6.4) is supplemented with boundary conditions

$$gn(x,t) - \varepsilon n_x(x,t)|_{x=0} = 0, \qquad t > 0, \tag{4.6.5}$$
$$n(x,0) = n_0(x). \tag{4.6.6}$$

In this case, $\varepsilon > 0$ is the dispersion coefficient, $g > 0$ is the growth rate of the cells, $b > 0$ the division rate, $\mu \geq 0$ the death rate and $\alpha > 1$ the number of daughter cells produced by the division of one parent cell. The SSDs of Equation (4.6.4) with boundary condition (4.6.5) (and additional assumptions about the decay of the solution as $x \to \infty$) were studied in [68].

From [30] we know of the existence of a solution u to the problem

$$0 = gy'(x) - \alpha by(\alpha x) + \alpha by(x),$$

satisfying both boundary conditions (4.6.2) and (4.6.3). This problem is merely (4.6.1) with $\varepsilon = 0$. The solution u is given by

$$u(x) = \frac{a}{K} \int_0^x \sum_{n=0}^{\infty} \frac{(-1)^n \alpha^n e^{-a\alpha^n s}}{(\alpha - 1)(\alpha^2 - 1) \dots (\alpha^n - 1)} \, ds, \tag{4.6.7}$$

with $a = \alpha b/g$ and

$$K = \prod_{n=1}^{\infty} (1 - \alpha^{-n}).$$

In the case of (4.6.4) we know that the overall population of cells grows or decays like $e^{[b(\alpha-1)-\mu]t}$. Hence, we can transform the growth/decay out of (4.6.4) by examining $m = ne^{-[b(\alpha-1)-\mu]t}$ and looking for a steady-state. The problem (4.6.1) comes from looking for a steady-state of the equation governing

$$M(x,t) = \int_0^x m(\xi, t) \, d\xi.$$

Thus, as has been mentioned, we are examining cumulative SSDs rather than SSDs. An example of the regular SSD and the corresponding cumulative SSD, representing $u(x)$, is shown in Figure 4.1.

An important inequality which is used in the rest of the section is,

$$|u''(x)| \leq Ce^{-ax},$$

where $C > 0$ is some constant. This inequality is the result of the fact that the sum in (4.6.7), and the corresponding sum of derivatives and double derivatives, converges absolutely.

Theorem 4.6.1. *There exist positive constants M_1, M_2 and M_3 such that for*

$$0 < \varepsilon < \frac{g^2(\sqrt{\alpha} - 1)}{3b\sqrt{\alpha}} \tag{4.6.8}$$

there is a solution $y = y(x, \varepsilon)$ to (4.6.1) satisfying (4.6.2), (4.6.3) and

$$|y(x,\varepsilon) - u(x)| \leq 2\varepsilon A(\varepsilon) \begin{cases} \sqrt{x}, & 0 \leq x \leq x_0(\varepsilon), \\ \frac{x_0(\varepsilon)}{\sqrt{x}}, & x > x_0(\varepsilon), \end{cases}. \tag{4.6.9}$$

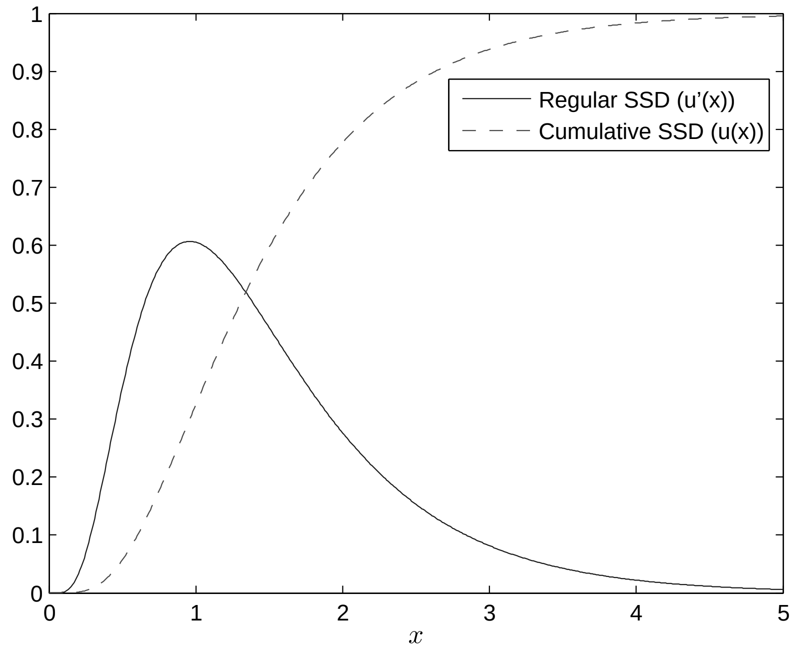


Figure 4.1: Cumulative and regular SSDs for parameters $\alpha = 2$, $b = 2$, $g = 3$ and $\varepsilon = 0$. The cumulative SSD shows what $u(x)$ (as given in Equation (4.6.7)) looks like.

where

$$0 < x_0(\varepsilon) = \frac{g}{2b(\sqrt{\alpha}-1)} - \frac{2C\sqrt{g}}{A(\varepsilon)\sqrt{\alpha}[2b(\sqrt{\alpha}-1)]^{1.5}}, \tag{4.6.10}$$

and

$$A(\varepsilon) = \max\left\{\frac{M_1}{M_2 - M_3\sqrt{\varepsilon}}, \frac{C}{\sqrt{2\alpha bg(\sqrt{\alpha}-1)}}(1+\sqrt{\alpha - 2\sqrt{\alpha}+2})\right\}. \tag{4.6.11}$$

Explicit values for M_1, M_2 and M_3 are given in Section 4.9 by (4.9.2), (4.9.3) *and* (4.9.4) *respectively.*

Practically, the above theorem means that as $\varepsilon \to 0^+$ the error between the cumulative SSD $u(x)$ for zero dispersion and the cumulative SSD for dispersion coefficient ε is uniformly $O(\varepsilon)$. Wake et al. [68] proved the existence and uniqueness of SSDs for non-zero values of ε, along with the fact that as $\varepsilon \to 0^+$ the Dirichlet series expression for those SSDs reduces to that of the SSD from [30]. Theorem 4.6.1 provides an error estimate for the difference of the cumulative SSDs for non-zero ε from the cumulative SSD for $\varepsilon = 0$.

Proof. For any $A, x_0 > 0$ define

$$\gamma(x,\varepsilon) = A\varepsilon \begin{cases} \sqrt{x}, & 0 \le x \le x_0, \\ \frac{x_0}{\sqrt{x}}, & x > x_0. \end{cases}$$

It will be shown that for sufficiently small ε there are values of A and x_0 such that,

$$\phi(x,\varepsilon) = u(x) - \gamma(x,\varepsilon), \qquad \psi(x,\varepsilon) = u(x) + \gamma(x,\varepsilon)$$

are lower and upper λ-solutions to (4.6.1) respectively, on any interval $[c,\infty)$, $c > 0$. The focus will be on proving that ψ is an upper λ-solution since the proof that ϕ is a lower λ-solution proceeds similarly. The inequalities which arise in the case of ϕ are, in fact, exactly the same as those which we deal with in the case of ψ.

Consider the problem of finding an appropriate value for x_0 given A. When $x \le x_0/\alpha$ we have

$$\frac{\varepsilon\psi''}{\gamma} = \frac{u''}{A\sqrt{x}} - \frac{\varepsilon}{4x^2} \le \frac{C}{A\sqrt{x}}e^{-ax},$$
$$(g\psi' - \alpha b\psi(\alpha x,\varepsilon) + \alpha b\psi)/\gamma = \frac{g}{2x} + \alpha b(1-\sqrt{\alpha}).$$

Therefore a sufficient condition for $\psi(x,\varepsilon)$ to be an upper λ-solution in the region $c \le x \le x_0/\alpha$ is that

$$\alpha b(\sqrt{\alpha}-1)x + \frac{C}{A}\sqrt{x} - \frac{g}{2} \le 0. \tag{4.6.12}$$

By the quadratic formula it can be seen that when

$$x \le \left(\frac{-C/A + \sqrt{(C/A)^2 + 2g\alpha b(\sqrt{\alpha}-1)}}{2\alpha b(\sqrt{\alpha}-1)}\right)^2,$$

$\psi(x,\varepsilon)$ is an upper λ-solution. Thus, we shall choose

$$x_0 \le \alpha\left(\frac{-C/A + \sqrt{(C/A)^2 + 2g\alpha b(\sqrt{\alpha}-1)}}{2\alpha b(\sqrt{\alpha}-1)}\right)^2.$$

We may express the above requirement on x_0 as

$$x_0 \le \frac{g}{2b(\sqrt{\alpha}-1)} - \delta_0, \tag{4.6.13}$$

where δ_0 is a function of A such that

$$0 < \delta_0 < \frac{2C\sqrt{g}}{A\sqrt{\alpha}[2b(\sqrt{\alpha}-1)]^{1.5}}. \tag{4.6.14}$$

We choose x_0 to be the right-hand-side of (4.6.13) with the upper bound of δ_0 from (4.6.14) substituted into the expression. It will be shown that this choice also yields an upper λ-solution on $x_0/\alpha < x < x_0$, since then the forward looking nonlocal term $\psi(\alpha x, \varepsilon)$ is not equal to $u(\alpha x) + A\varepsilon\sqrt{\alpha x}$ and we therefore have a different inequality to satisfy than (4.6.12). We thus choose x_0 as follows:

$$x_0 = \frac{g}{2b(\sqrt{\alpha}-1)} - \frac{2C\sqrt{g}}{A\sqrt{\alpha}[2b(\sqrt{\alpha}-1)]^{1.5}}. \tag{4.6.15}$$

To ensure that $x_0 > 0$ we must have

$$A > \frac{C}{\sqrt{2\alpha bg(\sqrt{\alpha}-1)}}. \tag{4.6.16}$$

In Section 4.8, it is shown that a sufficient condition for $\psi(x, \varepsilon)$ to also be an upper λ-solution in the region $x_0/\alpha \leq x \leq x_0$ is

$$A \geq \frac{C}{\sqrt{2\alpha bg(\sqrt{\alpha}-1)}}\left(1 + \sqrt{\alpha - 2\sqrt{\alpha}+2}\right). \tag{4.6.17}$$

This gives the second restriction in (4.6.11). Note that this choice of A produces a non-negative x_0 given that $\alpha > 1$.

We now turn our attention to the second part of $\gamma(x, \varepsilon)$. When $x \geq x_0$ we have

$$\frac{\varepsilon\psi''}{\gamma} = \frac{u''\sqrt{x}}{Ax_0} + \frac{3\varepsilon}{4x^2} \leq \frac{C\sqrt{x}}{Ax_0}e^{-ax} + \frac{3\varepsilon}{4x^2},$$
$$(g\psi' - \alpha b\psi(\alpha x, \varepsilon) + \alpha b\psi)/\gamma = -\frac{g}{2x} + \sqrt{\alpha}b(\sqrt{\alpha}-1).$$

Therefore a sufficient condition for $\psi(x, \varepsilon)$ to be an upper λ-solution in the region $x > x_0$ is that,

$$x \geq \frac{g}{2\sqrt{\alpha}b(\sqrt{\alpha}-1)} + \frac{Cx^{1.5}}{Ax_0\sqrt{\alpha}b(\sqrt{\alpha}-1)}e^{-ax} + \frac{3\varepsilon}{4x\sqrt{\alpha}b(\sqrt{\alpha}-1)}, \tag{4.6.18}$$

for all $x > x_0$.

A and ε need to be chosen so that x_0 satisfies (4.6.18). It is easily found that

$$\max_{x>0} \frac{Cx^{1.5}}{Ax_0\sqrt{\alpha}b(\sqrt{\alpha}-1)}e^{-ax} = \frac{1.5^{1.5}Ce^{-1.5}}{Ax_0ab\sqrt{a\alpha}(\sqrt{\alpha}-1)} = \frac{C'}{Ax_0ab\sqrt{a\alpha}(\sqrt{\alpha}-1)},$$

where $C' = 1.5^{1.5}Ce^{-1.5}$.

Given any $\varepsilon > 0$ we now desire an A such that the positive solution x_1 to

$$x = \frac{g}{2\sqrt{\alpha}b(\sqrt{\alpha}-1)} + \frac{C'}{Ax_0ab\sqrt{a\alpha}(\sqrt{\alpha}-1)} + \frac{3\varepsilon}{4x\sqrt{\alpha}b(\sqrt{\alpha}-1)} \tag{4.6.19}$$

is less than or equal to x_0; since then when $x > x_1$, condition (4.6.18) will be satisfied. We find that $x_1 \leq x_0$, and hence that $\psi(x, \varepsilon)$ is an upper λ-solution for $x > x_0$, when

$$A \geq \frac{M_1}{M_2 - M_3\sqrt{\varepsilon}}, \tag{4.6.20}$$

where M_1, M_2 and M_3 are positive constants given in Section 4.9 by (4.9.2), (4.9.3) and (4.9.4) respectively. Moreover, it can be seen in Section 4.9 that a positive choice of A is only possible when $0 < \varepsilon < (M_2/M_3)^2$. Calculating $(M_2/M_3)^2$ in terms of the parameters of the problem gives the restriction (4.6.8). Similarly, when these conditions on A and ε are satisfied then $\phi(x,\varepsilon)$ will be a lower λ-solution on any interval $[c,\infty)$, $c > 0$. Moreover assumptions (A_1), (A_2), (A_4) and (B) hold for the problem at hand.

Therefore, by Theorem 4.3.5 we find that on any interval $[c,\infty)$, $c > 0$, a solution $y_c(x,\varepsilon)$ exists to (4.6.1) such that $\phi(x) \leq y_c(x,\varepsilon) \leq \psi(x)$ for all $x \in [c,\infty)$. Let us form a sequence of intervals $[1/z_n, z_n]$ with $0 < z_1 < z_2 < \ldots$. Then in a similar way to the proof of Theorem 4.3.5, we can construct a sequence of functions $y_m(x,\varepsilon)$ which converge uniformly on any given interval $[1/z_n, z_n]$ to a limit function $y(x)$ satisfying (4.6.1) on $(0,\infty)$. Moreover, $\phi(x) \leq y(x,\varepsilon) \leq \psi(x)$ for all $x \in (0,\infty)$.

Now, it can be seen that $\phi(x), \psi(x) \to 0$ as $x \to 0$. Therefore, $y(x,\varepsilon) \to 0$ as $x \to 0$. Hence, if we let $y(0,\varepsilon) = 0$ we will have constructed a solution of (4.6.1) in the space $C^2(0,\infty) \cap C[0,\infty)$, satisfying the boundary condition (4.6.2) and the error estimate (4.6.9). It can also be seen that the solution $y(x,\varepsilon)$ satisfies the boundary condition (4.6.3) since from [30] we know that $u(x) \to 1$ as $x \to \infty$ and by the error estimate (4.6.9), $y(x,\varepsilon) \to u(x)$ as $x \to \infty$.

Finally, by taking account of the restrictions (4.6.20) and (4.6.17) for A, we find that x_0 and A are given by (4.6.10) and (4.6.11) respectively. This completes the proof of Theorem 4.6.1. $\square$

4.7 Functional extension of the upper/lower solution theory

In this section it is shown that the above results can apply in the situation where $y^*(x)$ has a more general form than $(y \circ \lambda)(x)$. We wish to include such terms as

$$y^*(x) = \int_I b(x,\xi) y(\xi)\ d\xi,$$

which, as was pointed out in Section 1.4, in the setting of cell growth and division can be used to represent asymmetric cell-division, where a single cell divides into unequally sized daughter cells. The terms $(y \circ \lambda)(x)$ are thus replaced by terms $\Theta(x,y)$ for some functional Θ. Where above we considered λ-solutions, we now consider Θ-solutions. We require that Θ satisfy some conditions to ensure that similar arguments may be applied. For example, we wish that for any given x, $\Theta(x,y)$ should not depend on the value of $y(\xi)$ outside of some finite interval.

First, the analogue of Theorem 4.2.5 (Theorem 4.7.1) is proved. Following this, the analogues of Lemmas 4.3.2, 4.3.3 and Theorem 4.3.4 (Lemmas 4.7.3, 4.7.4 and Theorem 4.7.5) are stated without proof, since the proofs in this case are almost identical to the proofs where λ-solutions are considered. The analogue of Theorem 4.3.5 (Theorem 4.7.6) is then stated with a given proof, while the analogue of Theorem 4.3.6 is stated without proof.

4.7.1 Auxiliary theorem

Here Theorem 4.7.1, the analogue of Theorem 4.2.5, is proved.

Let I be a compact interval and $|\cdot|$ be any norm on $\mathbb{R}^d$, $d > 0$. Let f and the sequence $f_1, f_2, \ldots$ be continuous functions defined on $(x, y, y^*) \in I \times \mathbb{R}^d \times \mathbb{R}^d = E$, mapping E into $\mathbb{R}^d$, such that the assumptions (H_1)-(H_3) from Section 4.2 hold.

As in Section 4.2, where we had a sequence of functions λ_n which converged uniformly to some limit $\Lambda(x)$, we have in this case a sequence of functionals Θ_n which converge in some sense to a limiting functional Θ. This sequence of functionals Θ_n is described below, along with sufficient assumptions for Theorem 4.7.1 to hold.

Let $\Theta(x, y)$ and the sequence $\Theta_1(x, y), \Theta_2(x, y), \ldots$ be continuous functionals mapping $I \times [L^\infty(I)]^d$ to $\mathbb{R}^d$. We say the functionals are continuous in the sense that, for any $y_0(x)$ and $\varepsilon > 0$, there exists a $\delta > 0$ such that when

$$||y - y_0||_\infty = \sup_{x \in I} |y(x) - y_0(x)| < \delta; \qquad |x_1 - x_2| < \delta$$

we have

$$|\Theta(x_1, y) - \Theta(x_2, y_0)| < \epsilon,$$

and the same holds when Θ is replaced by Θ_i.

Let $NS(\Theta(x, \cdot)) \subset \mathbb{R}$ be the set of reals such that when the support of y is contained in $NS(\Theta(x, \cdot))$,

$$\Theta(x, y) = \Theta(x, 0).$$

We define the support of $\Theta(x, \cdot)$ to be the complement of the set $NS(\Theta)$ and denote this set by $\mathrm{supp}(\Theta(x, \cdot))$. Further, for any subset $A \subset \mathbb{R}$ we denote

$$\mathrm{supp}(\Theta(A, \cdot)) = \bigcup_{x \in A} \mathrm{supp}(\Theta(x, \cdot)).$$

Define the norm

$$||\Theta||_\infty = \sup_{x \in I; y \in (C(I))^d} \frac{|\Theta(x, y)|}{||y||_\infty}.$$

Assume that the sequence of functionals Θ_n is bounded in the norm defined above and that for any $y : I \to \mathbb{R}^d$,

$$||\Theta_n - \Theta||_\infty \to 0$$

as $n \to \infty$. Moreover, let

$$\mathrm{supp}(\Theta_n(x,\cdot)) \subset \mathrm{supp}(\Theta(x,\cdot))$$

for all $n \geq 1$, $x \subset I$ and let $\mathrm{supp}(\Theta(A,\cdot))$ be compact for all compact $A \subset I$.

Then we have the following result:

Theorem 4.7.1. *Let there be given a sequence $(x_n, y_{n0}) \to (x_0, y_0) \in I \times \mathbb{R}^d$ as $n \to \infty$ and a sequence of functions $y_1(x), y_2(x), \ldots$ each defined on an interval containing I such that*

$$y_n'(x) = f_n(x, y_n(x), \Theta_n(x, y_n)), \qquad y(x_n) = y_{n0}$$

for all $x \in I$.

Let $A \subset I$ be an interval such that $A \subset I$ with

$$supp(\Theta(A,\cdot)) \subset I,$$

and assume that A contains a neighbourhood of x_0.

Then there is a function $y(x)$ defined on I such that

$$y' = f(x, y, \Theta(x,y)), \qquad y(x_0) = y_0, \tag{4.7.1}$$

for all $x \in A$. Moreover, there is a sequence of integers $n_1 < n_2 < \ldots$ such that

$$y_{n_k}(x) \to y(x)$$

uniformly on I as $k \to \infty$.

Proof. **There is a limit function:** This part of the proof is the same as in the proof of Theorem 4.2.5.

The limit is a solution: Let $A \subset I$ be an interval containing an open neighbourhood of x_0, with $\Lambda(A) \subset I$. Since A is compact and $\mathrm{supp}(\Theta(x,\cdot)), \mathrm{supp}(\Theta_n(x,\cdot)) \subset I$ for all $x \in A$, we find that for some constant C,

$$|\Theta_n(x, y_n)| \leq ||\Theta_n(x, y_n)||||y_n||_\infty \leq C$$

for all $n \geq 1$. This is due to the boundedness of the sequence Θ_n and the uniform boundedness of the sequence y_n on I. Therefore, the sequence of functions

$$y_n^*(x) = \Theta_n(x, y_n)$$

is uniformly bounded on A. Similarly, it can be shown that $y^*(x) = \Theta(x, y)$ is bounded by the same bound.

Let B be the uniform bound of $|y_n(x) - y_0|$ on A and B^* be the uniform bound of $|y_n^*(x) - y_0|$ on A. The functions f, f_n, $n \geq 1$ are continuous, and are thus uniformly continuous on any compact set. Hence, they are uniformly continuous on

$$U = \{(x, y, y^*) : |y - y_0| \leq B, |y^* - y_0| \leq B^*, x \in A\},$$

with $(x, y(x), y^*(x)), (x, y_n(x), y_n^*(x)) \in U$ for all $x \in A$ and $n \geq 1$. By Lemma 4.2.3 and (H_1) the functions f, $\{f_n\}$ are uniformly bounded on U. It will now be shown that $y(x)$ satisfies (4.7.1) on A.

For $x \in A$, consider

$$\mathcal{E}(x) = \left| y(x) - y_0 - \int_{x_0}^{x} f(s, y(s), \Theta(s, y))\, ds \right|.$$

By the uniform continuity of f on U, the uniform convergence of y_n to y on I and the continuity of Θ, we find that for any $\varepsilon_1 > 0$ there exists an integer $N_1 > 0$ such that for all $n \geq N_1$ we have

$$\mathcal{E}(x) \leq \left| y(x) - y_0 - \int_{x_0}^{x} f(s, y_n(s), \Theta(s, y_n))\, ds \right| + \varepsilon_1.$$

By the convergence of Θ_n to Θ on A, and the uniform continuity of f on U, we find that for any $\varepsilon_2 > 0$ there exists an integer $N_2 > N_1$ such that for all $n \geq N_2$ we have

$$\mathcal{E}(x) \leq \left| y(x) - y_0 - \int_{x_0}^{x} f(s, y_n(s), \Theta_n(s, y_n))\, ds \right| + \sum_{k=1}^{2} \varepsilon_k.$$

By the uniform convergence of f_n to f on U we find that for any $\varepsilon_3 > 0$ there exists some $N_3 > N_2$ such that for all $n \geq N_3$ we have

$$\mathcal{E}(x) \leq \left| y(x) - y_0 - \int_{x_0}^{x} f_n(s, y_n(s), \Theta_n(s, y_n))\, ds \right| + \sum_{k=1}^{3} \varepsilon_k.$$

By the convergence of (x_n, y_{n0}) to (x_0, y_0) and the uniform boundedness of all f_n on U, we find that for any $\varepsilon_4 > 0$ there exists an $N_4 > N_3$ such that for all $n \geq N_4$ we have $x_n \in A$ and

$$\begin{aligned} \mathcal{E}(x) &\leq \left| y(x) - y_{n0} - \int_{x_n}^{x} f_n(s, y_n(s), \Theta_n(s, y_n))\, ds \right| + \sum_{k=1}^{4} \varepsilon_k, \\ &= |y(x) - y_n(x)| + \sum_{k=1}^{4} \varepsilon_k. \end{aligned}$$

Finally, by the uniform convergence of y_n to y on A we find that for any $\varepsilon_5 > 0$ there exists an $N_5 > N_4$ such that for all $n \geq N_5$ we have

$$\mathcal{E}(x) = \left| y(x) - y_0 - \int_{x_0}^{x} f(s, y(s), \Theta(s, y))\, ds \right| \leq \sum_{k=1}^{5} \varepsilon_k.$$

And since the ε_k, $k \in \{1, 2, 3, 4, 5\}$ are arbitrary it follows that $y(x)$ is a solution to (4.7.1) on A. This completes the proof of Theorem 4.7.1. $\square$

4.7.2 Main results restated

We begin here by stating the definition of upper, lower and regular Θ-solutions. The key results from Section 4.3 are then restated for this new notion of Θ-solutions. A proof is given for only one result: Theorem 4.7.6. The proofs of the other results are almost the same as the proofs of their analogues in Section 4.3.

Definition 4.7.2. *Let I and J be intervals with $J \supset I$ and $\Theta(x, y)$ be a continuous functional such that supp$(\Theta(I, \cdot)) \subset J$.*

1. *A C^2 function ϕ on the interval J is said to be a* lower Θ-solution *of* (4.1.1) *on I if*

$$\phi''(x) \geq f(x, \phi(x), \Theta(x, \phi), \phi'(x))$$

for all $x \in I$.

2. *A C^2 function ψ on the interval J is said to be an* upper Θ-solution *of* (4.1.1) *on I if*

$$\psi''(x) \leq f(x, \psi(x), \Theta(x, \psi), \psi'(x))$$

for all $x \in I$.

3. *A C^2 function y on the interval J is said to be a* Θ-solution *of* (4.1.1) *on I if*

$$y''(x) = f(x, y(x), \Theta(x, y), y'(x))$$

for all $x \in I$.

The analogues of Lemmas 4.3.2, 4.3.3 and Theorem 4.3.4 follow similarly for Θ-solutions as they did for λ-solutions. They are stated below without proof.

Lemma 4.7.3. *Let $f(x, y, y^*, y')$ be continuous on $[a, b] \times \mathbb{R}^3$ and $\Theta(x, y)$ be a continuous functional, in the sense described at the beginning of Section 4.7.1 ,such that supp$(\Theta(I, \cdot)) \subset I$. Let there exist a constant $M > 0$ such that*

$$|f(x, y, y^*, y')| \leq M,$$

for all $(x, y, y^*, y') \in [a, b] \times \mathbb{R}^3$. Then the boundary value problem (4.1.1), (4.1.2) *and* (4.1.3) *has a Θ-solution, (under the relaxed restrictions on p_i, q_i in Section 4.5).*

We shall say that Θ is positive, if

$$\Theta(x, y) \geq \Theta(x, z),$$

when $y(x) \geq z(x)$ for all $x \in I$.

Lemma 4.7.4. *Let the I and J be intervals; $I = [a, b]$, $J \supset I$; $\Theta(x, y)$ and $\Delta(x, y)$ be positive continuous functionals such that*

$$supp(\Theta(I, \cdot)) \subset J; \qquad supp(\Delta(I, \cdot)) \subset I,$$

and let $f(x, y, y^*, y')$ be defined as in Lemma 4.7.3. Let ϕ, ψ be lower/upper Θ-solutions of (4.1.1) *on I respectively, such that (A_1)-(A_4) hold. Define*

$$G(x, y, y^*, y') = \begin{cases} f(x, y, \psi^*(x), y'), & \psi^*(x) < y^*, \\ f(x, y, y^*, y'), & \phi^*(x) \leq y^* \leq \psi^*(x), \\ f(x, y, \phi^*(x), y'), & y^* < \phi^*(x), \end{cases}$$

where $\phi^*(x) = \Theta(x, \phi)$ and $\psi^*(x) = \Theta(x, \psi)$. (Note that since Θ is positive, we have $\phi^*(x) \leq \psi^*(x)$ for all $x \in I$.)

Then there exists a Δ-solution y on the interval I to the boundary value problem

$$y'' = G(x, y, y^*, y'), \tag{4.7.2}$$

with boundary conditions (4.1.2) *and* (4.1.3)*, such that $\phi(x) \leq y(x) \leq \psi(x)$ for all $x \in I$. Furthermore if $\Delta(x, y) = \Theta(x, y)$ for all continuous functions $y : I \to \mathbb{R}$ and $x \in I$, then y is a Θ-solution to* (4.1.1) *on I.*

Theorem 4.7.5. *Let $I = [a, b]$ and let $f(x, y, y^*, y')$ be continuous on $I \times \mathbb{R}^3$. Let $\Theta(x, y)$ be a positive continuous functional, in the sense described at the beginning of Section 4.7.1, such that $supp(\Theta(I, \cdot)) \subset I$ and let $\phi(x)$ and $\psi(x)$ be lower and upper Θ-solutions to* (4.1.1) *respectively. Assume that (A_1)-(A_4) and (B) hold. Then there exists a Θ-solution y to* (4.1.1) *with boundary conditions* (4.1.2) *and* (4.1.3) *such that $\phi(x) \leq y(x) \leq \psi(x)$ for all $x \in I$.*

We now turn our attention to the analogue of Theorem 4.3.5:

Theorem 4.7.6. *Let $I = [a, \infty)$ and let $f(x, y, y^*, y')$ be continuous in $I \times \mathbb{R}^3$. Let $\Theta(x, y)$ be a positive continuous functional, in the sense described at the beginning of Section 4.7.1, such that $supp(\Theta(A, \cdot))$ is compact for all compact $A \in I$ and let ϕ and ψ be lower and upper Θ-solutions to* (4.1.1) *respectively. Assume (A_1),(A_2),(A_4) and (B) hold. Then there exists a Θ-solution $y(x)$ to* (4.1.1) *with boundary condition* (4.1.2) *such that $\phi(x) \leq y(x) \leq \psi(x)$ for all $x \in I$.*

Proof. Let $a_n = a + n$ for all $n \geq 1$ and form the sequence of intervals $I_n = [a, a_n]$, $n = 1, 2, \ldots$. Form the corresponding sequence of intervals $J_n = [a, b_n]$, $n = 1, 2, \ldots$, where

$$b_n = \max\{\max\ \operatorname{supp}(\Theta(I_n, \cdot)), a_n\}.$$

The maximum point of $\operatorname{supp}(\Theta(I_n, \cdot)$ exists since we have assumed that $\operatorname{supp}(\Theta(A, \cdot))$ is compact for any compact subset A of I.

We then have $\operatorname{supp}(\Theta(I_n, \cdot)) \subset J_n$ for all $n \geq 1$. Finally, form the sequence of values π_n, $n = 1, 2, \ldots$, such that $\phi(b_n) \leq \pi_n \leq \psi(b_n)$ for all $n \geq 1$. Define $\Theta_n(x, y)$, $n \geq 1$, as

$$\Theta_n(x, y) = \Theta(x, y_{J_n}),$$

where

$$y_{J_n}(x) = \begin{cases} y(x), & x \in J_n, \\ 0, & \text{otherwise.} \end{cases}$$

Note that $\Theta_n(x, y) = \Theta(x, y)$ on the interval I_n since $\operatorname{supp}(\Theta(I_n, \cdot)) \subset J_n$.

For each interval J_n, let N, F_N and F_1 be defined as in the proof for Theorem 4.3.4 (but here $\phi^*(x) = \Theta(x, \phi)$ and $\psi^*(x) = \Theta(x, \psi)$). From Lemma 4.7.4 it follows that the boundary value problem

$$y'' = F_N(x, y, y^*, y'),$$
$$p_0 y(a) - q_0 y'(a) = A, \qquad y(b_n) = \pi_n,$$

has a Θ_n-solution y_N on J_n with $\phi(x) \leq y_N(x) \leq \psi(x)$ for all $x \in J_n$. Using the similar reasoning as in Theorem 4.3.4, we see that the functions F_N satisfy (H_1)-(H_3), the conditions necessary for the use Theorem 4.7.1. Pick x_N so that $y_N(b_n) - y_N(a) = (b_n - a)y'_N(x_N)$. It then follows (as in Theorem 4.3.4) that the sequences $\{x_N\}$, $\{y_N(x_N)\}$ and $\{y'_N(x_N)\}$ are bounded and so by consecutively picking convergent subsequences and using Theorem 4.7.1, we conclude that there is a Θ_n-solution y_n of

$$y'' = F_1(x, y, y^*, y'),$$
$$p_0 y(a) - q_0 y'(a) = A, \qquad y(b_n) = \pi_n,$$

such that $\phi(x) \leq y_n(x) \leq \psi(x)$ for all $x \in J_n$. Moreover, since $\Theta_n = \Theta$ on I_n we find that y_n is a Θ-solution on the interval I_n.

Now, for any interval J_n consider the constant sequence of functions $F_1, F_1, \ldots$. This is uniformly convergent on all compact sets in $I \times \mathbb{R}^3$ to F_1. Moreover, on the interval J_n,

$$F_1(x, y, y^*, y') = F_1(x, y, \gamma(x, y^*), y'),$$

where $\gamma(x, y^*)$ is defined as in Theorem 4.3.4 (again with $\phi^*(x) = \Theta(x, \phi)$ and $\psi^*(x) = \Theta(x, \psi)$) . Furthermore, from (B) and the construction of F_1, we know that

$$|F_1(x, y, y^*, y')| = O(||(y, y')||_2)$$

as $||(y, y')||_2 \to \infty$ uniformly over $\{(x, y^*) : x \in J_n, y* \in \gamma(J_n, \mathbb{R})\}$. Finally, the sequence of functionals $||\Theta_n - \Theta||_\infty \to 0$ on all intervals J_n with

$$\text{supp}(\Theta_n(x, \cdot)) \subset \text{supp}(\Theta(x, \cdot))$$

for all $x \in J_n$. Thus (H_1)-(H_3) are satisfied (when we extend F_1 to a system of first order differential equations), along with the assumptions on the sequence Θ_n in Theorem 4.2.5 on any interval J_n. We shall now find a suitable sequence of solutions of initial-value problems converging uniformly on all compact sets in I.

All solutions y_m for $m \geq n+1$ are defined on the interval $J_n = [a, b_n]$ and by the mean value theorem we may pick $x_{nm} \in [a, b_n]$ such that

$$y_m(b_n) - y_m(a) = (b_n - a)y_m'(x_{nm}).$$

Thus the sequence $y_m'(x_{nm})$, $m = n+1, n+2, \ldots$ is bounded in a similar way to (4.3.8) from Theorem 4.3.4.

For $n = 1$ we may consecutively pick subsequences as m varies of

$$\{x_{nm}\}, \qquad \{y_m(x_{nm})\}, \qquad \{y_m'(x_{nm})\}$$

which converge. It then follows from Theorem 4.7.1 that there is a subsequence of $\{y_m\}$, denoted by S_1 which converges on the interval J_1 to a Θ-solution of (4.1.1) on the interval I_1 satisfying the boundary condition (4.1.2). If we repeat this process for each interval J_n, and at each step take subsequences of the appropriate previous subsequences, we may form the sequence of subsequences

$$S_1 \supset S_2 \supset S_3 \supset \ldots,$$

with the subsequence S_n converging on J_n to a Θ-solution of (4.1.1) on the interval I_n satisfying the boundary condition (4.1.2). Taking the diagonal sequence S_d from $S_1, S_2, \ldots$, we then have a subsequence of $\{y_n\}_{n=1}^{\infty}$ which converges to a Θ-solution y of (4.1.1) such that $\phi(x) \leq y(x) \leq \psi(x)$ on all compact intervals in $[a, \infty)$. Furthermore, as in Theorem 4.3.4, the limit function y satisfies the boundary condition (4.1.2). $\square$

Finally, we have the analogue of Theorem 4.3.6:

Theorem 4.7.7. *Let $I = (-\infty, \infty)$ and let $f(x, y, y^*, y')$ be continuous in $I \times \mathbb{R}^3$. Let $\Theta(x, y)$ be a positive continuous functional, in the sense described at the beginning of Section 4.7.1, such that supp$(\Theta(A, \cdot))$ is compact for all compact $A \subset I$ and let ϕ and ψ be lower and upper Θ-solutions to* (4.1.1) *respectively. Assume (A_1),(A_4) and (B) hold. Then there exists a Θ-solution $y(x)$ to* (4.1.1) *such that $\phi(x) \leq y(x) \leq \psi(x)$ for all $x \in I$.*

The proof of the Theorem 4.7.7 is similar to the proof of Theorem 4.7.6. It differs from the proof of Theorem 4.7.6 in the same way that the proof if Theorem 4.3.6 differs from the proof of Theorem 4.3.5.

The same comments regarding generalised lower/upper λ-solutions hold when regarding lower/upper Θ-solutions. Moreover, the restrictions on p_0, q_0, p_1 and q_1 (which determine the boundary conditions of the problem (4.1.1)-(4.1.3)) are the same relaxed conditions which were introduced in the case of λ-solutions in Section 4.5.

4.7.3 Functional example: Integral kernel

As was mentioned at the start of this section, we wish to be able to deal with terms such as

$$y^*(x) = \int_I b(x, \xi) y(\xi) \, d\xi,$$

when dealing with the problem (4.1.1)-(4.1.3) on the interval I. Thus, we let

$$\Theta(x, y) = \int_I b(x, \xi) y(\xi) \, d\xi, \tag{4.7.3}$$

for some interval $I \subset \mathbb{R}$. In order that Theorems 4.7.5, 4.7.6 and 4.7.7 hold we must have

$$\text{supp}(\Theta(I, \cdot)) \subset I,$$

and, in the case that I is infinite, we need supp$(\Theta(A, \cdot))$ compact for any compact $A \subset I$. Obviously the first condition is satisfied; that is, since the integral in Equation (4.7.3) is over I, the support of $\Theta(x, \cdot)$ is contained in I.

Consider now the requirement that supp$(\Theta(A, \cdot))$ be compact for any compact $A \subset I$. From the definition of $\Theta(x, y)$, we see that we must then have

$$\bigcup_{x \in A} \text{supp } b(x, \cdot)$$

compact for all compact $A \subset I$. This will be satisfied by, for example a Gaussian distribution, truncated at three standard deviations from the mean, with mean x. This is because the support of $b(x, \cdot)$ will be compact, with continuously varying endpoints for the region of support.

We also require that Θ is positive and continuous. In order to ensure that Θ is positive in the case of Equation (4.7.3), we can just assume that $b(x,\xi) \geq 0$ for all $x, \xi \in I$.

For $\Theta(x,y)$ to be continuous it is required that for a given $y_0(x)$ and $\varepsilon > 0$ there must exist a $\delta > 0$ such that

$$|\Theta(x,y) - \Theta(x_0,y_0)| < \varepsilon$$

when $||y - y_0||_\infty < \delta$ and $|x - x_0| < \delta$. From Equation (4.7.3) we require

$$|\Theta(x,y) - \Theta(x_0,y_0)| = \left|\int_I b(x,\xi)y(\xi) - b(x_0,\xi)y_0(\xi)\ d\xi\right| < \varepsilon.$$

Now, we know that

$$\left|\int_I b(x,\xi)y(\xi) - b(x_0,\xi)y_0(\xi)\ d\xi\right| \leq \int_I b(x,\xi)|y(\xi) - y_0(\xi)| + y_0(\xi)|b(x,\xi) - b(x_0,\xi)|\ d\xi.$$

Thus $|\Theta(x,y) - \Theta(x_0,y_0)| < \varepsilon$ if

$$\int_I b(x,\xi)|y(\xi) - y_0(\xi)| + y_0(\xi)|b(x,\xi) - b(x_0,\xi)|\ d\xi < \varepsilon. \tag{4.7.4}$$

If we restrict $b(x,\xi)$ to being uniformly continuous and bounded, it is possible to choose $\delta > 0$ such that when $||y - y_0||_\infty < \delta$ and $|x - x_0| < \delta$, the inequality 4.7.4 is satisfied.

Less restrictive conditions on $b(x,\xi)$ are certainly possible, but it may be easier to check on a case by case basis whether the function $b(x,\xi)$ produces a positive continuous functional Θ.

4.8 Sufficient conditions for the construction in Theorem 4.6.1 to yield an upper solution in the region $x_0/\alpha \leq x \leq x_0$

In this section it is shown that a sufficient condition for $\psi(x,\varepsilon)$ from Theorem 4.6.1 to be an upper λ-solution in the region $x_0/\alpha \leq x \leq x_0$ is (4.6.17)

We start by noting that for $x_0/\alpha \leq x \leq x_0$ we have

$$(g\psi' - \alpha b\psi(\alpha x,\varepsilon) + \alpha b\psi)/\gamma = \frac{g}{2x} + \alpha b - \frac{\sqrt{\alpha} b x_0}{x}. \tag{4.8.1}$$

This leads us to conclude that a sufficient condition for ψ to be an upper λ-solution on $x_0/\alpha \leq x \leq x_0$ is that

$$-\alpha b x + \frac{C}{A}\sqrt{x} - \frac{g}{2} + \sqrt{\alpha} b x_0 \leq 0. \tag{4.8.2}$$

When $x = x_0/\alpha$, the above inequality reduces to (4.6.12) and is therefore satisfied at x_0/α. Consider now the derivative of the left-hand-side of the above inequality. We see that, for $x \geq x_0/\alpha$ it is equal to

$$-\alpha b + \frac{C}{2A\sqrt{x}} \leq -\alpha b + \frac{C\sqrt{\alpha}}{2A\sqrt{x_0}}.$$

Hence, if the right hand side of the above expression is less than or equal to zero, ψ will be an upper λ-solution on $x_0/\alpha \leq x \leq x_0$. After some manipulation, this sufficient condition is expressed as

$$\frac{4A^2 x_0}{C^2\alpha} - \frac{1}{\alpha^2 b^2} \geq 0. \tag{4.8.3}$$

Substituting in our choice of x_0, from (4.6.15), to the above equation gives a quadratic inequality, which in turn, on dividing by the coefficient of A^2 becomes

$$A^2 - \frac{2CA}{\sqrt{2\alpha bg(\sqrt{\alpha}-1)}} - \frac{C^2(\sqrt{\alpha}-1)}{2\alpha bg} \geq 0. \tag{4.8.4}$$

It can now be seen that ψ will be an upper λ-solution in the region $x_0/\alpha \leq x \leq x_0$ when A is greater than or equal to the positive root of the above quadratic inequality. After some manipulation of the positive root, this condition may be expressed as in (4.6.17).

4.9 Technical working for the constants M_1, M_2 and M_3 in Theorem 4.6.1

Here the working to find M_1, M_2 and M_3 from (4.6.20) is set out. Let,

$$P = \frac{g}{2\sqrt{\alpha}b(\sqrt{\alpha}-1)} + \frac{C'}{Ax_0 ab\sqrt{a\alpha}(\sqrt{\alpha}-1)}, \qquad Q = \frac{3\varepsilon}{4\sqrt{\alpha}b(\sqrt{\alpha}-1)}.$$

Note that since $x_0 > 0$, both P and Q are positive. Thus, by the quadratic formula the positive solution of (4.6.19) is

$$x_1 = \frac{P + \sqrt{P^2 + 4Q}}{2} \leq P + \sqrt{Q}.$$

We now look for a range of A such that $P + \sqrt{Q} \leq x_0$ is satisfied. Writing P out in full and rearranging this inequality we find that it is satisfied if and only if

$$\frac{C'}{ab\sqrt{a\alpha}(\sqrt{\alpha}-1)} \leq Ax_0^2 - \frac{gAx_0}{2\sqrt{\alpha}b(\sqrt{\alpha}-1)} - Ax_0\sqrt{Q}. \tag{4.9.1}$$

Substituting in our choice of x_0 from (4.6.15), we find that the right-hand-side of (4.9.1) is greater than

$$\begin{aligned} &\frac{Ag^2}{4b^2(\sqrt{\alpha}-1)^2} - \frac{4Cg^{1.5}}{\sqrt{\alpha}[2b(\sqrt{\alpha}-1)]^{2.5}} + \frac{4C^2 g}{A\alpha[2b(\sqrt{\alpha}-1)]^3} \\ &\qquad - \frac{g^2 A}{4\sqrt{\alpha}b^2(\sqrt{\alpha}-1)^2} - \frac{gA\sqrt{3\varepsilon}}{4\alpha^{0.25}[b(\sqrt{\alpha}-1)]^{1.5}}. \end{aligned}$$

From this it can be seen that (4.9.1) is satisfied when

$$\begin{aligned} A \quad \geq \quad & \left(\frac{C'}{ab\sqrt{a\alpha}(\sqrt{\alpha}-1)} + \frac{4Cg^{1.5}}{\sqrt{\alpha}[2b(\sqrt{\alpha}-1)]^{2.5}}\right) \\ & / \left(\frac{g^2}{4b^2\sqrt{\alpha}(\sqrt{\alpha}-1)} - \frac{g\sqrt{3\varepsilon}}{4\alpha^{0.25}[b(\sqrt{\alpha}-1)]^{1.5}}\right). \end{aligned}$$

This supplies us with values of M_1, M_2 and M_3 as follows:

$$M_1 = \frac{C'}{ab\sqrt{a\alpha}(\sqrt{\alpha}-1)} + \frac{4Cg^{1.5}}{\sqrt{\alpha}[2b(\sqrt{\alpha}-1)]^{2.5}}, \tag{4.9.2}$$

$$M_2 = \frac{g^2}{4b^2\sqrt{\alpha}(\sqrt{\alpha}-1)}, \tag{4.9.3}$$

$$M_3 = \frac{g\sqrt{3}}{4\alpha^{0.25}[b(\sqrt{\alpha}-1)]^{1.5}}. \tag{4.9.4}$$

Note, however, that in the derivation of the inequality $A \geq \frac{M_1}{M_2 - M_3\sqrt{\varepsilon}}$ a division by $(M_2 - M_3\sqrt{\varepsilon})$ is performed. Thus, if $M_2 - M_3\sqrt{\varepsilon} < 0$, the sign of the inequality is reversed and a positive choice for A is not possible. Therefore we see that a positive choice for A is only possible when $0 < \varepsilon < (M_2/M_3)^2$.

Chapter 5

Analysis of a multi-compartment age-distribution model of cell growth

In this chapter we cover a model of the age-distribution of cells in each of the three phases: G_1, S and G_2, of eukaryotic cell growth (see Chapter 1 for a brief explanation of the phases of cell growth). Age is considered to be the time spent by a given cell in its current phase. Thus, each cell has age zero when entering into a new phase of cell growth. There is no compartment in this model corresponding to M-phase. Effectively this means that M-phase is lumped together with G_2-phase. This is mainly for mathematical simplicity.

5.1 The model

The model covered in this section is a simplification of those studied in [15, 61], in the context of cancer chemotherapy, which have extra compartments (for example, both [15] and [61] include a G_0-phase). The governing equation in the present context is

$$\frac{\partial n(\tau,t)}{\partial t}+\frac{\partial n(\tau,t)}{\partial \tau}=-D_{out}(\tau,t)n(\tau,t), \tag{5.1.1}$$

with boundary condition at $\tau=0$:

$$n(0,t)=\int_0^\infty D_{in}(\tau)n(\tau,t)\ d\tau. \tag{5.1.2}$$

The function $n(\tau,t)$ in this case is a vector quantity, with

$$n(\tau,t)=[G_1(\tau,t),S(\tau,t),G_2(\tau,t)]^T.$$

For example, $G_1(\tau,t)$ represents the density of cells that have spent τ time in G_1 phase at time t. The matrix D_{out} represents the loss of cells from the various phases via death and transfer to other phases and is defined as,

$$D_{out}(\tau,t) = \begin{bmatrix} k_{G_1}(\tau,t)+\mu_{G_1}(\tau,t) & 0 & 0 \\ 0 & k_S(\tau,t)+\mu_S(\tau,t) & 0 \\ 0 & 0 & k_{G_2}(\tau,t)+\mu_{G_2}(\tau,t) \end{bmatrix}, \tag{5.1.3}$$

where the terms k_p, $p \in \{G_1, S, G_2\}$ represent the transfer rates out of the phases G_1, S, G_2 and into the phases S, G_2 and G_1 respectively, and μ_p, $p \in \{G_1, S, G_2\}$ represent the death rates.

The matrix D_{in} represents the gain of cells at age $\tau = 0$ in each phase, due to transfer from other phases. D_{in} is defined as,

$$D_{in}(\tau) = \begin{bmatrix} 0 & 0 & 2k_{G_2}(\tau,t) \\ k_{G_1}(\tau,t) & 0 & 0 \\ 0 & k_S(\tau,t) & 0 \end{bmatrix}. \tag{5.1.4}$$

Assumptions: It is assumed that $k_p, \mu_p \in C[0,\infty)$ for all $p \in \{G_1, S, G_2\}$, with k_p bounded and positive. We also assume that $k_p(\tau,t)$ and $\mu_p(\tau,t)$ are uniformly continuous for all $p \in \{G_1, S, G_2\}$ and that they have bounded, continuous derivatives in τ and t. Finally, assume that there exists some $\mathcal{M} > 0$ such that $k_p(\tau,t) + \mu_p(\tau,t) \geq \mathcal{M}$ for all $p \in \{G_1, S, G_2\}$ and $(\tau,t) \in [0,\infty) \times [0,\infty)$. We shall use $n_p(\tau,t)$, $p \in \{G_1, S, G_2\}$ to denote the component of $n(\tau,t)$ associated with the phase p. When p occurs in a summation formula, we use $p+1$ to signify the following:

$$G_1 + 1 = S; \qquad S + 1 = G_2; \qquad G_2 + 1 = G_1.$$

The initial distribution is prescribed as

$$n(\tau,0) = n_0(\tau), \tag{5.1.5}$$

with each component of $n_0(\tau)$ in $(L^1 \cap L^\infty)[0,\infty)$.

Definition 5.1.1. *The problem described by Equations* (5.1.1)-(5.1.5) *shall henceforth be referred to as Problem P.*

In the following analysis, it may be the case that certain derivatives such as $\frac{\partial}{\partial t}n(\tau,t)$ do not exist. We shall therefore always identify the differential operator

$$\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}$$

with the operator

$$\frac{\partial}{\partial \rho},$$

under the characteristic coordinate system (ξ, ρ), where

$$\xi = \tau - t, \qquad \rho = t,$$

and the characteristic projections of the solution n are described by

$$t = \rho; \qquad \tau = \xi + t.$$

In the following we use $n(\tau, t)$ and $n(\xi, \rho)$ interchangeably, considering (ξ, ρ) to denote the same point as (τ, t). Identifying the above operators in the way we have described means that we can solve (5.1.1) along characteristic lines to obtain a solution which satisfies the differential equation for all $(\tau, t) \in [0, \infty) \times [0, \infty)$.

Some examples of papers on age-structured models are to be found in [28, 36, 69, 52]: In [28] and [36], age-distribution models with a nonlinear terms depending on population size are studied. Local stability of steady age-distributions is shown in [28], while [36] shows global stability for the model studied therein. In [52], global asymptotic stability is shown for a linear age-distribution model. [69] presents a population model structured by age and some other variable, and shows global asymptotic stability under certain restrictions on the birth process. All of the models dealt with above are single-compartment models, with birth and death terms independent of time. We deal here with a simple model, but with multiple compartments, and we allow the birth and death terms to depend on both age and time.

In this chapter, we first examine the existence of solutions to problem P in Section 5.2. Some preliminary results which are needed to determine the asymptotic behaviour of solutions to problem P are then given in Section 5.3. Stability results for the model with periodic coefficients and periodic solutions are given in Section 5.4. In Section 5.5, we assume D_{out} and D_{in} are independent of time and show the existence of steady age-distributions, $N(\tau)$, to problem P. Steady age-distributions, $N(\tau)$, give solutions to problem P of the form

$$n(\tau, t) = e^{\lambda t} N(\tau), \tag{5.1.6}$$

for some $\lambda \in \mathbb{R}$. These solutions are found to be stable due to the results from Section 5.4. Finally, in Section 5.6, time-dependency is introduced for the matrices D_{in} and D_{out}, so that they are dependent both on τ and t. It is assumed that they are T-periodic for some $T > 0$ and the question of whether there are solutions to problem P of the form

$$n(\tau, t) = e^{\lambda t} m(\tau, t), \tag{5.1.7}$$

with $m(\tau, t)$ being T-periodic, is investigated (again, these are stable due to the results of Section 5.4).

Note that in Section 5.5 and 5.6, we work with modified problems $P(\lambda)$ and $P^*(\lambda)$ (these are defined at the beginning of Section 5.5). Any steady-state solution, $N(\tau)$ of $P(\lambda)$ is a steady age-distribution for problem P. Thus if $N(\tau)$ solves problem $P(\lambda)$, then $e^{\lambda t}N(\tau)$ solves problem P. Moreover, any periodic solution, $m(\tau,t)$ of $P(\lambda)$, gives a solution of the form (5.1.7) to problem P. So while it may seem at first glance that we are not attempting to find solutions of the form (5.1.6) and (5.1.7) to problem P in Sections 5.5 and 5.6, this is merely because we are working with transformed problems and concentrating on finding the $N(\tau)$ in (5.1.6) or the $m(\tau,t)$ in (5.1.7).

5.2 Existence of a unique solution to problem P

We now investigate whether any solution exists to problem P. Proceding formally, solving the governing differential equation, (5.1.1), of problem P along characteristic lines gives

$$n(\tau,t) = \begin{cases} \exp\left(-\int_0^\tau D_{out}(s,s+t-\tau)\ ds\right) n(0,t-\tau), & 0 \le \tau < t, \\ \exp\left(-\int_{\tau-t}^\tau D_{out}(s,s+t-\tau)\ ds\right) n_0(\tau-t), & t \le \tau. \end{cases} \tag{5.2.1}$$

This assumes that the solution on the boundary $\tau = 0$ has been given. However, in problem P we are given the renewal boundary condition (5.1.2). Substituting the formal solution from (5.2.1) into the boundary condition (5.1.2) gives us a Volterra integral equation of the second kind for $n(0,t)$:

$$n(0,t) = \mathcal{F}(t) + \int_0^t K(s,t) n(0,s)\ ds, \tag{5.2.2}$$

where

$$\begin{aligned} \mathcal{F}(t) &= \int_t^\infty D_{in}(\tau,t) \exp\left(-\int_{\tau-t}^\tau D_{out}(s,s+t-\tau)\ ds\right) n_0(\tau-t)\ d\tau, \\ K(s,t) &= D_{in}(t-s,t) \exp\left(-\int_0^{t-s} D_{out}(\xi,\xi+s)\ d\xi\right). \end{aligned}$$

Now, by the assumptions made in problem P we know that $D_{out}(\tau,t)$ and $D_{in}(\tau,t)$ are uniformly continuous. Therefore $K(s,t)$ is continuous. Moreover, since the components of $n_0(\tau)$ are in $(L^1 \cap L^\infty)[0,\infty)$ and the components of $D_{in}(\tau,t)$ are bounded, we find that $\mathcal{F}(t)$ exists. We also find, by the uniform continuity of D_{out} and D_{in}, that $\mathcal{F}(t)$ is continuous. Thus we may apply Theorem 3.11 of [45], which tells us that there is a unique continuous solution to Equation (5.2.2) on $[0,T]$ for any $T > 0$. Moreover, since $\mathcal{F}$ and K all have non-negative components, the solution $n(0,t)$ must also be non-negative (use a successive approximation argument with $\mathcal{F}(t)$ as a first approximation).

We now examine the integrability of the solution $n(\tau, t)$. First, we see that on any region $[0, \infty) \times [0, T]$, $T > 0$, the magnitude $n_p(\tau, t)$, $p \in \{G_1, S, G_2\}$, is bounded by

$$\max\left\{\sup_{0<t<T} n_p(0,t), \text{ess-sup}_{0<\tau<\infty} n_{0,p}(\tau)\right\}.$$

Thus $n_p(\tau, t) \in L^\infty([0, \infty) \times [0, T])$ for any $T > 0$.

Moreover we find that

$$\begin{aligned}\int_0^T \int_0^\infty |n_p(\tau,t)| \; d\tau \; dt \leq T \int_0^\infty n_{0,p}(\tau) \; d\tau \\ + \int_0^T \int_0^t n_p(0, t-\tau) \exp\left(-\int_0^\tau k_p(s, s+t-\tau) + \mu_p(s, s+t-\tau)\right) \; ds,\end{aligned}$$

and since we assumed that each component of n_0 is in $L^1[0, \infty)$, we can conclude that

$$\int_0^T \int_0^\infty |n_p(\tau,t)| \; d\tau \; dt < \infty$$

for any $T > 0$, $i \in \{1, 2, 3\}$. This implies that each component of $n(\tau, t)$ belongs to $L^1([0, \infty) \times [0, T])$.

In a similar way to the above, we also find that each component of $n(\cdot, t)$ belongs to $(L^1 \cap L^\infty)[0, \infty)$ for all $t \geq 0$.

The above results are summarised in the following theorem:

Theorem 5.2.1. *There exists a unique solution $0 \leq n(\tau, t)$ (along characteristic lines) to problem P such that each component of $n(\tau, t)$ belongs to $(L^1 \cap L^\infty)([0, \infty) \times [0, T])$ for any $T > 0$, and each component of $n(\cdot, t)$ belongs to $(L^1 \cap L^\infty)[0, \infty)$ for all $t \geq 0$.*

We now state a simple result which follows from the linearity of problem P.

Lemma 5.2.2. *Let $n(\tau, t)$ and $m(\tau, t)$ be two solutions to problem P with differing initial conditions $n_0(\tau)$ and $m_0(\tau)$. If $0 \leq n_0(\tau) \leq Cm_0(\tau)$ for some constant C, then the solution to P corresponding to the initial distribution $n_0(\tau)$ satisfies $0 \leq n(\tau, t) \leq Cm(\tau, t)$ for all $t \geq 0$.*

Proof. The problem P is linear, so any linear combination of solutions will also be a solution. $Cm(\tau, t) - n(\tau, t)$ has non-negative initial condition $Cm_0(\tau) - n_0(\tau)$. Thus $Cm(\tau, t) - n(\tau, t)$ will be a non-negative solution of P. $\square$

Before moving on, we shall prove two results regarding the first partial derivatives of $n(\tau, t)$.

Lemma 5.2.3. *Let $n(\tau, t)$ be the unique solution of problem P. Then given any $T > 0$, we find that each component of $n_t(\tau, t)$ belongs to $L^\infty([0, \tau_0] \times [t_0, t_0 + T])$ for $t_0 > \tau_0$.*

Proof. Let $|n(\tau,t)|$ be the vector formed by taking absolute values of each component of $n(\tau,t)$. From Equation (5.2.1), we find that, for $t_0 > \tau_0$,

$$|n_t(\tau,t)| = e^{-\int_0^\tau D_{out}(s,s+t-\tau)\ ds} \left| n_t(0,t-\tau) - \left[\int_0^\tau \frac{\partial}{\partial t} D_{out}(s,s+t-\tau)\ ds\right] n(0,t-\tau) \right|. \quad (5.2.3)$$

for all $(\tau,t) \in [0,\tau_0] \times [t_0, t_0+T]$.

From Equation (5.2.2) we find that

$$n_t(0,t) = \mathcal{F}'(t) + K(t,t)n(0,t) + \int_0^t K_t(s,t)n(0,s)\ ds, \quad (5.2.4)$$

and we calculate $\mathcal{F}'(t)$, using a change in variables, to be

$$\mathcal{F}'(t) = \int_0^\infty \left[\frac{\partial}{\partial t} D_{in}(\tau+t,t) - D_{in}(\tau+t,t)D_{out}(\tau+t,t)\right] e^{-\int_\tau^{\tau+t} D_{out}(s,s-\tau)\ ds} n_0(\tau)\ d\tau.$$

Due to the assumptions regarding the differentiability and boundedness of the coefficients $k_p(\tau,t)$ and $\mu_p(\tau,t)$ we find that the components of $\mathcal{F}'(t)$ are bounded for $t \geq 0$ and also that the components of $K_t(s,t)$ are bounded for all $t \geq 0$ and $0 \leq s \leq t$. Therefore $n_t(0,t-\tau)$ exists and is bounded for $t \leq t_0 + T$, $\tau < t$. Moreover, since $n(0,t-\tau)$ is continuous and $\frac{\partial}{\partial t} D_{out}(s,s+t-\tau)$ has bounded components, we find, using Equation (5.2.3), that $|n_t(\tau,t)|$ is bounded for $(\tau,t) \in [0,\tau_0] \times [t_0,t_0+T]$ when $t_0 > \tau_0$. □

We now examine the integrability of the partial derivatives of n for a bounded age-range and large enough time. This is important in Lemma 5.4.1, Section 5.4.

Lemma 5.2.4. *If each component of $n(0,t)$ is bounded for all $t \geq 0$ then for any $T > 0$, each component of $n(\tau,t)$ belongs to $W^{1,q}([0,\tau_0] \times [t_0,t_0+T])$ (the Sobolev space of functions in $L^q([0,\tau_0] \times [t_0,t_0+T])$ with first weak derivatives in the same space) for any $q \geq 1$ when $t_0 > \tau_0$, with $||n_p||_{W^{1,q}([0,\tau_0]\times[t_0,t_0+T])}$, $p \in \{G_1, S, G_2\}$ bounded by a constant for all $t_0 > \tau_0$.*

Proof. From Equation (5.2.1), it follows immediately that when $n(0,t)$ is bounded for all $t \geq 0$, then $n(\tau,t)$ belongs to $L^\infty([0,\tau_0] \times [t_0,t_0+T])$ for all $t_0 > \tau_0$. But then, since $[0,\tau_0] \times [t_0,t_0+T]$ is a bounded, we find that each component of $n(\tau,t)$ belongs to $L^q([0,\tau_0] \times [t_0,t_0+T])$.

Now, from the previous theorem it can be seen that for $t_0 > \tau_0$, we have each component of $n_t(\tau,t)$ in $L^\infty([0,\tau_0] \times [t_0,t_0+T])$. From Equation (5.1.1), we then find that each component of $n_\tau(\tau,t)$ is in $L^\infty([0,\tau_0] \times [t_0,t_0+T])$. Combining this fact with what we found in the previous paragraph, we find that each component of $n(\tau,t)$ belongs to $W^{1,q}([0,\tau_0] \times [t_0,t_0+T])$.

To show that $||n_p(\tau,t)||_{W^{1,q}([0,\tau_0]\times[t_0,t_0+T])}$, $p \in \{G_1,S,G_2\}$ is bounded by a constant for all $t_0 > \tau_0$, consider Equation (5.2.3). There we see that since $n(0,t)$ is bounded for all $t \geq 0$, we need only to show the boundedness of $n_t(0,t)$ to prove that each component of $n_t(\tau,t)$ is bounded for $(\tau,t) \in [0,\tau_0] \times (\tau_0,\infty)$. This would show that $n_\tau(\tau,t)$ is also bounded for $(\tau,t) \in [0,\tau_0] \times (\tau_0,\infty)$. Thus the boundedness of $n_t(0,t)$ for $t \geq 0$ implies that $||n_p(\tau,t)||_{W^{1,q}([0,\tau_0]\times[t_0,t_0+T])}$, $p \in \{G_1, S, G_2\}$ is bounded by a constant for all $t_0 > \tau_0$. We shall now attempt to show that $n_t(0,t)$ is bounded for $t \geq 0$.

Consider now Equation (5.2.4). We know from the proof of the previous theorem that $\mathcal{F}'(t)$ is bounded for $t \geq 0$. Moreover, we know that $K(t,t)n(0,t)$ is bounded for $t \geq 0$ by the assumptions on the coefficients k_p and μ_p, $p \in \{G_1, S, G_2\}$ and the assumption regarding $n(0,t)$ in the statement of this lemma.

It remains to show that the vector

$$\begin{aligned}&\int_0^t K_t(s,t)n(0,s)\ ds\\ &= \int_0^t \left(\frac{\partial}{\partial t}D_{in}(t-s,t) - D_{in}(t-s,t)D_{out}(t-s,t)\right) e^{-\int_0^{t-s} D_{out}(\xi,\xi+s)\ d\xi} n(0,s)\ ds\end{aligned}$$

has bounded components. To show this, first note that the coefficients k_p and μ_p, $p \in \{G_1, S, G_2\}$, are bounded and have bounded derivatives. Moreover by the assumption of the theorem, $n(0,t)$ is bounded for all $t \geq 0$. Finally, note that since there is some constant $\mathcal{M} > 0$ such that $k_p(\tau,t) + \mu_p(\tau,t) \geq \mathcal{M}$ for all $p \in \{G_1, S, G_2\}$ and $(\tau,t) \in [0,\infty) \times [0,\infty)$, we find that for some constant $C > 0$,

$$\left|\left(\int_0^t K_t(s,t)n(0,s)\ ds\right)_p\right| \leq C\frac{1-e^{-t\mathcal{M}}}{\mathcal{M}}.$$

for all $p \in \{G_1, S, G_2\}$. Thus, each component of

$$\int_0^t K_t(s,t)n(0,s)\ ds$$

is bounded for all $t \geq 0$. As mentioned above, this completes the proof of the desired result. $\square$

5.3 Preliminary theory for proving the stability of the model

In this section we describe some result related to the asymptotic behaviour of the solution to problem P. We use a general relative entropy functional as in Chapter 3 and following [48, 49]; however, here we are working with a system of partial differential equations, rather than a single partial differential equation. The main useful result in this section is given in Lemma 5.3.4, which tells us how the functional $\mathcal{H}(n|m,\psi)(t)$ behaves as $t \to \infty$, where n and m are solutions of problem P with differing initial conditions, and ψ is the solution of the dual problem P^* defined as follows:

Definition 5.3.1. *We refer to the problem described by*

$$\begin{cases} \psi_t(\tau,t) + \psi_\tau(\tau,t) - D_{out}(\tau,t)\psi(\tau,t) + D_{in}^T(\tau,t)\psi(0,t) = 0, \\ \psi(\tau,t) \geq 0, \qquad \psi(\tau,t) \in L^\infty([0,\infty)\times[0,T]), \qquad T > 0, \end{cases} \tag{5.3.1}$$

where $\psi(0,t)$ is continuous for $t \geq 0$, as problem P^*.

Identifying the operator $\frac{\partial}{\partial t} + \frac{\partial}{\partial \tau}$ (in the natural coordinate system (τ,t)), with $\frac{\partial}{\partial \rho}$ (in characteristic coordinates), we can solve the above equation along characteristic lines, producing a solution which is continuous along characteristic lines and satisfies the differential equation for all $(\tau,t) \in [0,\infty)\times[0,\infty)$. We find the existence of solutions to problem P^*, under specific assumptions, in Sections 5.5 and 5.6 (by finding related solutions of problem $P^*(\lambda)$, defined in Section 5.5).

Note that we are considering the dual problem to P. This is in contrast to Chapter 3, where we work with the dual problem to the eigenvalue problem formed by replacing $n_t(\tau,t)$ with $\lambda n(\tau,t)$ in problem F. Thus ψ is dependent on time in this case. Similar to Chapter 3, we form the dual problem P in the following way:

Express Equation 5.1.1 as

$$n_t(\tau,t) = \mathcal{A}(t)n(\tau,t),$$

where $\mathcal{A}(t)$ is the differential operator $-\frac{\partial}{\partial \tau} - D_{out}(\tau,t)$. Then the dual problem is given by

$$\psi_t(\tau,t) = -\mathcal{A}^*(t)\psi(\tau,t),$$

where $\mathcal{A}^*(t)$ is defined such that

$$\int_0^\infty \psi^T(\tau,t)\mathcal{A}(t)n(\tau,t)\ d\tau = \int_0^\infty n^T(\tau,t)\mathcal{A}^*(t)\psi(\tau,t).$$

Using the notion of dual systems ([43] and Appendix B) we may say that $\mathcal{A}(t)$ and $\mathcal{A}^*(t)$ are adjoint with respect to the dual systems $\langle X_1, Y_1\rangle$ and $\langle X_2, Y_2\rangle$, where the bilinear form $\langle\cdot,\cdot\rangle$ is defined by

$$\langle f, g\rangle = \int_0^\infty f(\tau)g(\tau)\ d\tau,$$

with X_1, X_2, Y_1 and Y_2 defined as follows:

- X_1 is the set of vector valued functions $n(\tau)$ such that each component of n is in $W^{1,1}[0,\infty)$, the Sobolev space of functions in $L^1[0,\infty)$ whose first derivative is also in $L^1[0,\infty)$. Moreover n must satisfy the boundary condition (5.1.2).

- X_2 is the set of vector valued functions $n(\tau)$ such that each component of n is in $L^1[0,\infty)$

- Y_1 is the set of vector valued functions $\psi(\tau)$ such that each component of ψ is in $L^\infty[0,\infty)$.
- Y_2 is the set of vector valued functions $\psi(\tau)$ such that each component of ψ is in $W^{1,\infty}[0,\infty)$, the Sobolev space of functions in $L^\infty[0,\infty)$ whose first derivative is also in $L^\infty[0,\infty)$,

and X_1, X_2, Y_1, Y_2 are supplied with any suitable norms. $\mathcal{A}(t)$ maps X_1 to X_2, while $\mathcal{A}^*(t)$ maps Y_2 to Y_1. Thus

$$\langle \mathcal{A}(t)n, \psi\rangle = \langle n, \mathcal{A}^*(t)\psi\rangle \,,$$

for $n \in X_1$, $\psi \in Y_2$.

We require the following definition in what follows:

Definition 5.3.2. *Let $X^1(\rho_0)$ denote the set of functions which are absolutely integrable over the domain*

$$\{(\xi,\rho) : -\rho \le \xi < \infty;\ 0 \le \rho \le \rho_0\}.$$

Note that any function given in the characteristic coordinate system which is in $X^1(\rho_0)$ is in $L^1([0,\infty)\times[0,\rho_0])$ in the natural coordinate system (τ,t).

The following lemma summarises the relationship of the solution of the dual problem P^* to the solution of the problem P.

Lemma 5.3.3. *Let $n(\tau,t)$ and $m(\tau,t)$ be solutions of problem P with differing initial conditions*

$$n(\tau,0) = n_0(\tau); \qquad m(\tau,0) = m_0(\tau).$$

Let $\psi(\tau,t)$ be a solution of the dual problem P^* and let H be any continuously differentiable function. Then for $(\tau,t) \in [0,\infty)\times[0,\infty)$,

$$\begin{aligned}&\frac{\partial}{\partial t}\left[\psi_p(\tau,t)m_p(\tau,t)H\left(\frac{n_p(\tau,t)}{m_p(\tau,t)}\right)\right] + \frac{\partial}{\partial \tau}\left[\psi_p(\tau,t)m_p(\tau,t)H\left(\frac{n_p(\tau,t)}{m_p(\tau,t)}\right)\right] \\ &= -[D_{in}^T\psi(0,t)]_p m_p(\tau,t)H\left(\frac{n_p(\tau,t)}{m_p(\tau,t)}\right),\end{aligned} \tag{5.3.2}$$

where $p \in \{G_1, S, G_2\}$. Moreover

$$\int_0^\infty \psi^T(\tau,t)n(\tau,t)\ d\tau = \int_0^\infty \psi_0^T(\tau)n_0(\tau)\ d\tau, \tag{5.3.3}$$

and

$$\int_0^\infty \psi^T(\tau,t)|n(\tau,t)-m(\tau,t)|\ d\tau \le \int_0^\infty \psi_0^T(\tau)|n_0(\tau)-m_0(\tau)|\ d\tau, \tag{5.3.4}$$

for $t \ge 0$, where $|n-m|$ in the above equation denotes the vector formed by taking absolute values of each component of $n-m$.

Properties (5.3.3) and (5.3.4) are the analogues of the properties described in Theorems 3.2.1 and 3.2.2 from Chapter 3. They express constraints on the behaviour of n and m. In particular (5.3.4) is a restriction on how far apart n and m can grow in time. This time these properties are expressed in vector form. Another difference in the present case is that we have a dual solution $\psi(\tau, t)$ which varies with time as well as age, whereas in Chapter 3 the rules were expressed with a stationary $\psi(\tau)$. Working with a non-stationary dual solution is useful when we wish to prove the convergence of a solution to a periodic, rather than stationary attractor.

Proof. Equation (5.3.2) is derived via a straightforward calculation using the product and chain rules. Note that technically the calculation should be carried out in the characteristic coordinate system (ξ, ρ) before returning to the natural coordinates (τ, t).

We now show Equation (5.3.3). To achieve this we switch to the characteristic coordinate system:

$$\int_0^\infty \psi^T(\tau, t) n(\tau, t)\ d\tau = \int_{-\rho}^\infty \psi^T(\xi, \rho) n(\xi, \rho)\ d\xi$$

Assume that

$$\frac{\partial}{\partial \rho} \psi^T(\xi, \rho) n(\xi, \rho) \in X^1(\rho_0) \tag{5.3.5}$$

for any $\rho_0 > 0$, then, we can use Fubini's Theorem in the following to obtain

$$\begin{aligned}
\int_0^\rho \int_{-s}^\infty \frac{\partial}{\partial s} \psi^T(\xi, s) n(\xi, s)\ d\xi\ ds, &= \int_{-\rho}^\infty \int_{\max\{0,-\xi\}}^\rho \frac{\partial}{\partial s} \psi^T(\xi, s) n(\xi, s)\ ds\ d\xi \qquad \text{(Fubini)} \\
&= \int_{-\rho}^0 \psi^T(\xi, \rho) n(\xi, \rho) - \psi^T(\xi, -\xi) n(\xi, -\xi)\ d\xi \\
&\quad + \int_0^\infty \psi^T(\xi, \rho) n(\xi, \rho) - \psi^T(\xi, 0) n(\xi, 0)\ d\xi, \\
&= -C + \int_{-\rho}^\infty \psi^T(\xi, \rho) n(\xi, \rho)\ d\xi - \int_0^\rho \psi^T(-s, s) n(-s, s)\ ds,
\end{aligned}$$

where the above equations are all in characteristic coordinates, with

$$C = \int_0^\infty \psi^T(\xi, 0) n(\xi, 0)\ d\xi = \int_0^\infty \psi^T(\tau, 0) n(\tau, 0)\ d\tau.$$

Using the product rule we find that, for $\rho \geq 0$,

$$\frac{\partial}{\partial \rho} \psi^T(\xi, \rho) n(\xi, \rho) = -\psi^T(0, t) D_{in}(\tau, t) n(\tau, t),$$

where on the right-hand side we have used the natural coordinates (τ, t). The right hand side of the equation is in the space $L^1([0, \infty) \times [0, T])$ for any $T > 0$, since the components of ψ and D_{in} are bounded on $[0, \infty) \times [0, T]$. In characteristic coordinates the domain $\{(\tau, t) \in [0, \infty) \times [0, T]\}$ is given by $\{(\xi, \rho) \in [-\rho, \infty) \times [0, T]\} = X^1(T)$. Therefore the assumption (5.3.5) is satisfied.

We thus find that

$$\int_0^\infty \psi^T(\tau,t)n(\tau,t)\ d\tau = C + \int_0^\rho \int_{-s}^\infty \frac{\partial}{\partial s}\psi^T(\xi,s)n(\xi,s)\ d\xi + \psi^T(-s,s)n(-s,s)\ ds. \tag{5.3.6}$$

(where the right hand side is in characteristic coordinates) But we already know that

$$\int_{-\rho}^\infty \frac{\partial}{\partial \rho}\psi^T(\xi,\rho)n(\xi,\rho)\ d\xi = \int_0^\infty -\psi^T(0,t)D_{in}(\tau,t)n(\tau,t)\ d\tau = -\psi^T(0,t)n(0,t),$$

in the natural coordinates (τ, t), for all $t > 0$.

Now, the quantity $-\psi^T(0,t)n(0,t)$ is expressed in characteristic coordinates as $-\psi^T(-\rho,\rho)n(-\rho,\rho)$. Thus we find, using Equation (5.3.6), that

$$\int_0^\infty \psi^T(\tau,t)n(\tau,t)\ d\tau = C = \int_0^\infty \psi^T(\tau,0)n(\tau,0)\ d\tau,$$

for $t \geq 0$, which is what we desired.

Equation (5.3.4) is shown to hold in a similar way: Let $(n-m)(\tau,t) = g(\tau,t)$. It can be checked that, in characteristic coordinates, $|g|_\rho = -D_{out}(\xi,\rho)|g|(\xi,\rho)$. This comes from the fact that g satisfies the same equations as n and, from the explicit solution (5.2.1), we see that g has constant sign along the characteristic lines where ξ is held constant (recall that $\xi = \tau - t$).

Similarly to the above, we may now use Fubini's Theorem to obtain

$$\begin{aligned}
&\int_0^\infty \psi^T(\tau,t)|g|(\tau,t)\ d\tau = \int_{-\rho}^\infty \psi^T(\xi,\rho)|g|(\xi,\rho)\ d\xi \\
&= B + \int_0^\rho \left[\int_{-s}^\infty \frac{\partial}{\partial s}\psi^T(\xi,s)|g|(\xi,s)\ d\xi\right] + \psi^T(-s,s)|g|(-s,s)\ ds \\
&= B + \int_0^t \left[\int_0^\infty -\psi^T(0,s)D_{in}(\tau,s)|g|(\tau,s)\ d\tau\right] + \psi^T(0,s)|g|(0,s)\ ds
\end{aligned} \tag{5.3.7}$$

where we have switched from characteristic coordinates to natural coordinates between the second and third lines, and

$$B = \int_0^\infty \psi^T(\tau,0)|g|(\tau,0)\ d\tau.$$

Now, from the boundary condition (5.1.2) at $\tau = 0$, we know

$$|g(0,t)| = \left|\int_0^\infty D_{in}(\tau,t)g(\tau,t)\ d\tau\right| \leq \int_0^\infty D_{in}(\tau,t)|g|(\tau,t)\ d\tau.$$

for all $t > 0$. Therefore, using Equation (5.3.7), we obtain

$$\int_0^\infty \psi^T(\tau,t)|g|(\tau,t)\ d\tau \leq B = \int_0^\infty \psi^T(\tau,0)|g|(\tau,0)\ d\tau.$$

This completes the proof. $\square$

A lemma shall now be presented which has implications for the asymptotic behaviour of solutions to P. We use a general relative entropy functional $\mathcal{H}$ similar to that used in Chapter 3 to give us information about the difference between two solutions of problem P.

Lemma 5.3.4. *Let $n(\tau,t)$ and $m(\tau,t)$ be solutions of problem P with differing initial conditions $n_0(\tau)$, $m_0(\tau)$, and let $\psi(\tau,t)$ be a solution of the dual problem P^*. Let H be any non-negative convex function (see Definition C.0.5 in Appendix C) such that $H''(x) > 0$ and define*

$$\mathcal{H}(n|m,\psi)(t) = \sum_p \int_0^\infty \psi_p(\tau,t) m_p(\tau,t) H\left(\frac{n_p(\tau,t)}{m_p(\tau,t)}\right)\, d\tau, \tag{5.3.8}$$

$p \in \{G_1, S, G_2\}$. Assume that n is bounded by a constant multiple of m for all $t \geq 0$. Then $\mathcal{H}$ exists and is non-negative for all $t \geq 0$, with

$$\mathcal{H}_t = \frac{d}{dt}\mathcal{H}(n|m,\psi)(t) \leq 0,$$

where, specifically,

$$\begin{aligned}\mathcal{H}_t &= \sum_p \psi_{p+1}(0,t) \int_0^\infty a_p(\tau,t) m_p(\tau,t)\, d\tau \\ &\quad \times \int_0^\infty \left[H\left(\int_0^\infty \frac{n_p(y,t)}{m_p(y,t)} d\mu_t^p(y)\right) - H\left(\frac{n_p(\tau,t)}{m_p(\tau,t)}\right)\right] d\mu_t^p(\tau),\end{aligned} \tag{5.3.9}$$

$$d\mu_t^p(\tau) = \frac{a_p(\tau,t) m_p(\tau,t) d\tau}{\int_0^\infty a_p(\xi,t) m_p(\xi,t)\, d\xi}, \tag{5.3.10}$$

with $a_{G_1}(\tau,t) = k_{G_1}(\tau,t)$, $a_S(\tau,t) = k_S(\tau,t)$ and $a_{G_2}(\tau,t) = 2k_{G_2}(\tau,t)$.

Proof. First note that since n is bounded by a constant multiple of m, $H(n_p(\cdot,t)/m_p(\cdot,t)) \in L^\infty[0,\infty)$ for all $t \geq 0$. Moreover, since $\psi_p(\cdot,t) \in L^\infty[0,\infty)$ for all $t \geq 0$ and $m_p(\cdot,t) \in L^1[0,\infty)$ for all $t \geq 0$, we see that the integral in (5.3.8) must converge and that $\mathcal{H}(n|m,\psi)(t)$ is defined for all $t \geq 0$.

We now make use of the characteristic coordinates $\xi = \tau - t$ and $\rho = t$. Thus

$$\begin{aligned}\mathcal{H}_t &= \sum_p \frac{\partial}{\partial t} \int_0^\infty \psi_p(\tau,t) m_p(\tau,t) H\left(\frac{n_p(\tau,t)}{m_p(\tau,t)}\right)\, d\tau \\ &= \sum_p \frac{\partial}{\partial \rho} \int_{-\rho}^\infty \psi_p(\xi,\rho) m_p(\xi,\rho) H\left(\frac{n_p(\xi,\rho)}{m_p(\xi,\rho)}\right)\, d\xi.\end{aligned}$$

We aim now to show that Leibniz's rule can be applied: From Lemma 5.3.3, Equation (5.3.2), we find that

$$\frac{\partial}{\partial \rho}\psi_p(\xi,\rho) m_p(\xi,\rho) H\left(\frac{n_p(\xi,\rho)}{m_p(\xi,\rho)}\right) = -[D_{in}^T \psi(0,t)]_p m_p(\tau,t) H\left(\frac{n_p(\tau,t)}{m_p(\tau,t)}\right)$$

Since $m(\tau, t) \in L^1([0, \infty) \times [0, T])$ (by Theorem 5.2.1) and $n(\tau, t)$ is bounded by a constant multiple of $m(\tau, t)$, we find that the right hand side of the above equation is in $L^1([0, \infty) \times [0, T])$ for any $T > 0$. In characteristic coordinates the left hand side is therefore in $X^1(\rho_0)$ for any $\rho_0 > 0$.

Therefore we may apply Leibniz's rule to $\mathcal{H}_t$, which gives

$$\begin{aligned}
\mathcal{H}_t &= \sum_p \frac{\partial}{\partial \rho} \int_{-\rho}^{\infty} \psi_p(\xi, \rho) m_p(\xi, \rho) H\left(\frac{n_p(\xi, \rho)}{m_p(\xi, \rho)}\right) \, d\xi \\
&= \sum_p \psi_p(0, t) m_p(0, t) H\left(\frac{n_p(0, t)}{m_p(0, t)}\right) - \int_0^{\infty} [D_{in}^T(\tau, t)\psi(0, t)]_p m_p(\tau, t) H\left(\frac{n_p(\tau, t)}{m_p(\tau, t)}\right).
\end{aligned}$$

Where we have used Equation (5.3.2) from Lemma 5.3.3 again, and have substituted in the natural coordinates (τ, t) in the last line. Proceding from here, and using the fact that

$$m_p(0, t) = \int_0^{\infty} a_{p-1}(\tau, t) m_{p-1}(\tau, t) \, d\tau$$

it is found that

$$\begin{aligned}
\frac{d}{dt}\mathcal{H}(n|m, \psi)(t) = \sum_p \int_0^{\infty} & \psi_p(0, t) a_{p-1}(\tau, t) m_{p-1}(\tau, t) H\left(\frac{n_p(0, t)}{m_p(0, t)}\right) \\
& - \psi_{p+1}(0, t) a_p(\tau, t) m_p(\tau, t) H\left(\frac{n_p(\tau, t)}{m_p(\tau, t)}\right) \, d\tau.
\end{aligned}$$

Changing the order of summation gives

$$\frac{d}{dt}\mathcal{H}(n|m, \psi)(t) = \sum_p \psi_{p+1}(0, t) \int_0^{\infty} a_p(\tau, t) m_p(\tau, t) \left[H\left(\frac{n_{p+1}(0, t)}{m_{p+1}(0, t)}\right) - H\left(\frac{n_p(\tau, t)}{m_p(\tau, t)}\right)\right] \, d\tau.$$

Using the boundary condition (5.1.2) on $n_{p+1}(0, t)$ and $m_{p+1}(0, t)$, we find that Equation (5.3.9), in the statement of the theorem, follows. To see that $\mathcal{H}_t \leq 0$, note that for convex functions H, we have Jensen's Inequality (Appendix C):

$$\int_{\Omega} H(f(x)) \, d\mu(x) \geq H\left(\int_{\Omega} f(x) \, d\mu(x)\right),$$

where the $d\mu(x) = p(x)dx$ for some probability density function $p(x)$ on Ω. Thus

$$\int_0^{\infty} \left[H\left(\int_0^{\infty} \frac{n_p(y, t)}{m_p(y, t)} d\mu_t^p(y)\right) - H\left(\frac{n_p(\tau, t)}{m_p(\tau, t)}\right)\right] d\mu_t^p(\tau) \leq 0.$$

□

Lemma 5.3.4 has implications for the asymptotic behaviour of solutions to P because, given that $\mathcal{H}(n|m, \psi)(t) \geq 0$ for all $t \geq 0$ and is non-increasing with time, we must have $\int_t^{t+T} \mathcal{H}_t \, dt \to 0$ as $t \to \infty$. This fact is exploited in the following section.

5.4 Stability of positive periodic solutions to the model

For the bulk of this section we shall consider $n(\tau, t)$ and $m(\tau, t)$ to be two solutions to problem P with differing initial conditions $n_0(\tau)$ and $m_0(\tau)$ such that $n_0(\tau) \leq C m_0(\tau)$ for some constant C. This assumption will be lifted at the end of this section to give the convergence result (Theorem 5.4.5) for any $n_0(\tau)$ with (non-negative) components in $(L^1 \cap L^\infty)[0, \infty)$.

Let $\psi(\tau, t)$ be a solution to problem P^* scaled such that

$$\int_0^\infty \psi^T(\tau, t) m(\tau, t) \, d\tau = 1,$$

for all $t \geq 0$ (recall that the above integral is constant due to Lemma 5.3.3). We assume for the rest of this section that all coefficients k_p, μ_p and the solution pair $\psi(\tau, t)$ and $m(\tau, t)$ are periodic with period T_0. We also assume that $m(\tau, t)$ and $\psi(\tau, t)$ are strictly positive for all $(\tau, t) \in [0, \infty) \times [0, \infty)$. (The existence of such pairs of functions, $m(\tau, t)$ and $\psi(\tau, t)$, is studied in Section 5.6.)

It shall be shown that $n(\tau, t)$ tends to a constant multiple of $m(\tau, t)$, in the sense that

$$\int_0^\infty \psi^T(\tau, t) |n(\tau, t) - K^* m(\tau, t)| \, d\tau \to 0 \tag{5.4.1}$$

as $t \to \infty$ for some constant K^*.

Overview of the proof : Consider a sequence of times $0 \leq t_1 < t_2 < t_3 < \ldots$ such that $t_{k+1} = t_k + T_0$ for all $k \geq 1$. Let us consider the function $n(\tau, t)$ in the time intervals $t_k \leq t \leq t_k + T$, for some $T > 0$ (not necessarily equal to T_0). It turns out that we can pick a subsequence of times such that $n(\tau, t)$ tends to a limit function within these 'time-windows' $t_k \leq t \leq t_k + T$ (Lemma 5.4.1). We find that each component of this limit function, which we denote by $n^0(\tau, t)$, $0 \leq t \leq T$, is of the form $n_p^0(\tau, t) = \theta_p(t) m_p(\tau, t)$, $p \in \{G_1, S, G_2\}$ (Lemma 5.4.2). We then discover that $\theta_{G_1}(t) = \theta_S(t) = \theta_{G_2}(t) = K$ for some constant K and all $0 \leq t \leq T$ (Theorem 5.4.3).

This shows that for large t we should be able to find intervals $[t, t+T]$ where $n(\tau, t)$ is arbitrarily closely approximated by $Km(\tau, t)$. The properties (5.3.3) and (5.3.4) from Lemma 5.3.3 are then used to show that the limit of $n(\tau, t)$ as $t \to \infty$ (in the sense defined by Equation (5.4.1)) is indeed $Km(\tau, t)$, and that K is given by $\int_0^\infty \psi^T(\tau, 0) n_0(\tau) \, d\tau$ (Theorem 5.4.4 and 5.4.5).

Lemma 5.4.1. *Let n and m be solutions to the problem P, such that $n_0(\tau) \leq C m_0(\tau)$ for some $C > 0$, with m assumed to be periodic, as stated at the beginning of this section. Then, from Lemma 5.2.2, we must have $n(\tau, t) \leq C m(\tau, t)$ for all $t \geq 0$.*

Define

$$n^k(\tau, t) = n(\tau, t + t_k).$$

Then for any $T > 0$, there is a subsequence of times (denoted the same was as before) $0 \leq t_1 < t_2 < t_3 < \ldots$ such that $n_p^k(\tau, t) \to n_p^0(\tau, t)$, $p \in \{G_1, S, G_2\}$, in $L^1([0, \tau_0] \times [0, T])$ as $k \to \infty$ for any $\tau_0 > 0$ and some limiting function $n^0(\tau, t)$.

Moreover $0 \leq n_p^0(\tau, t) \in L^\infty([0, \tau_0] \times [0, T])$ for all $p \in \{G_1, S, G_2\}$ and $n_p^0(\tau, t)$ is bounded by a constant multiple of $m_p(\tau, t)$, with $[n_p^k(\tau, t)]^2 \to [n_p^0(\tau, t)]^2$ as $k \to \infty$ in $L^1([0, \tau_0] \times [0, T])$ for any $\tau_0 > 0$.

Finally,

$$\int_0^T \int_0^\infty |n_p^k(\tau, t) - n_p^0(\tau, t)| \, d\tau \, dt \to 0,$$

$p \in \{G_1, S, G_2\}$, as $k \to \infty$.

Proof. Take the sequence of times

$$0 \leq t_1; \qquad t_{k+1} = t_k + T_0, \quad k \geq 2.$$

Let $n^k(\tau, t) = n(\tau, t + t_k)$ for all integer $k \geq 1$. From Lemma 5.2.4 and the fact that $n^k(\tau, t)$ is bounded by a constant multiple of $m(\tau, t)$ (which is periodic, and therefore must be bounded due to Theorem 5.2.1), we find that the subsequence of functions n_p^k is bounded in $W^{1,1}([0, \tau_0] \times [0, T])$ for all $p \in \{G_1, S, G_2\}$. Thus, according to Rellich's Compactness Theorem [23], we find that there is a further subsequence of functions n^k with each component tending to a limit function in $L^1([0, \tau_0] \times [0, T])$. Thus there is some function $n^0(\tau, t)$ such that $n_p^k(\tau, t) \to n_p^0(\tau, t)$ in $L^1([0, \tau_0] \times [0, T])$ for all $p \in \{G_1, S, G_2\}$. Since τ_0 was arbitrary we may pick a sequence of subsequences $n^k(\tau, t)$ such that $n_p^k(\tau, t) \to n_p^0(\tau, t)$ in $L^1([0, \tau_0] \times [0, T])$ for a sequence of increasing values τ_0. Taking the diagonal sequence then gives the first convergence result stated in the theorem.

Each component $n_p^0(\tau, t)$ must be non-negative and bounded by $m_p(\tau, t)$, since if this were not so there would be a set of non-zero measure on which $|n_p^k(\tau, t) - n_p^0(\tau, t)| > \varepsilon$ for some $\varepsilon > 0$ and all $k \geq 1$. But then n_p^k would not converge to n_p^0 in $L^1([0, \tau_0] \times [0, T])$.

We now aim to show that $[n_p^k(\tau, t)]^2 \to [n_p^0(\tau, t)]^2$ as $k \to \infty$ in $L^1([0, \tau_0] \times [0, T])$ for any $\tau_0 > 0$. Note that

$$\int_0^T \int_0^{\tau_0} |[n_p^k(\tau, t)]^2 - [n_p^0(\tau, t)]^2| \, d\tau \, dt = \int_0^T \int_0^{\tau_0} |n_p^k(\tau, t) + n_p^0(\tau, t)||n_p^k(\tau, t) - n_p^0(\tau, t)| \, d\tau \, dt.$$

Now, since $|n_p^k(\tau, t) + n_p^0(\tau, t)|$ is bounded by $2m_p(\tau, t)$, and therefore is bounded in $[0, \tau_0] \times [0, T]$ by some constant M for all $k \geq 1$, we find that

$$\int_0^T \int_0^{\tau_0} |[n_p^k(\tau, t)]^2 - [n_p^0(\tau, t)]^2| \, d\tau \, dt \leq M \int_0^T \int_0^{\tau_0} |n_p^k(\tau, t) - n_p^0(\tau, t)| \, d\tau \, dt \to 0$$

as $k \to \infty$. This is the second convergence result stated in the theorem.

Consider now $\int_0^T \int_0^\infty |n_p^k(\tau,t) - n_p^0(\tau,t)|\ d\tau\ dt$, $p \in \{G_1, S, G_2\}$. Since $n_p^k(\tau,t)$ and $n_p^0(\tau,t)$ are bounded by a constant multiple of $m_p(\tau,t)$, we know that the sequence $|n_p^k(\tau,t) - n_p^0(\tau,t)|$ is bounded in $L^1([0,\infty)\times[0,T])$. Thus, for any $\varepsilon > 0$ we may pick τ_0 large enough such that

$$\int_0^T \int_{\tau_0}^\infty |n_p^k(\tau,t) - n_p^0(\tau,t)|\ d\tau\ dt < \varepsilon$$

for all $k \geq 1$. Following this we may pick $K > 0$ large enough such that

$$\int_0^T \int_0^{\tau_0} |n_p^k(\tau,t) - n_p^0(\tau,t)|\ d\tau\ dt < \varepsilon$$

for all $k \geq K$. We have thus shown that given any $\varepsilon > 0$ there exists some $K > 0$ such that

$$\int_0^T \int_0^\infty |n_p^k(\tau,t) - n_p^0(\tau,t)|\ d\tau\ dt < 2\varepsilon,$$

for all $k \geq K$. This proves the final convergence result in the statement of the theorem. $\square$

Now that we have found the limit function $n^0(\tau,t)$, we use Lemma 5.3.4 to show that each component $n_p^0(\tau,t)$ of n^0 is equal to $\theta_p(t)m_p(\tau,t)$ for some function θ_p of time. To summarise the proof: we find that the functional

$$\int_0^T \mathcal{H}_t(n^k|m,\psi)(t)\ dt \to \int_0^T \mathcal{H}_t(n^0|m,\psi)(t)\ dt$$

as $k \to \infty$. But as a consequence of Lemma 5.3.4, and the fact that m and ψ are periodic, we already know that $\int_0^T \mathcal{H}_t(n^k|m,\psi)(t)\ dt \to 0$ as $t \to \infty$. Therefore we must have $\int_0^T \mathcal{H}_t(n^0|m,\psi)(t)\ dt = 0$. Since $\mathcal{H}_t$ is non-positive, this implies that $\mathcal{H}_t(n^0|m,\psi)(t) = 0$ for $0 \leq t \leq T$. This is only satisfied when $n_p^0(\tau,t) = \theta_p(t)m_p(\tau,t)$ for all $p \in \{G_1, S, G_2\}$. More detail is to be found in the proof below.

Note that it has not yet been shown that the limit function $n^0(\tau,t)$ behaves like the limit as $t \to \infty$ of $n(\tau,t)$. The function $n^0(\tau,t)$ is merely the limiting behaviour of n within the chosen sequence of time-windows $t_k \leq t \leq t_k + T$ as $k \to \infty$.

Lemma 5.4.2. *Define $n^k(\tau,t)$ in the same way as in Lemma 5.4.1, with $n_p^k(\tau,t)$, $k = 1,2,\ldots$ having limit $n_p^0(\tau,t)$ in $L^1([0,\infty)\times[0,T])$ for each $p \in \{G_1, S, G_2\}$. Then $n_p^0(\tau,t) = \theta_p(t)m_p(\tau,t)$ for some functions $\theta_p(t)$, $p \in \{G_1, S, G_2\}$.*

Proof. Let $T > 0$ be fixed and choose $H(x) = x^2$ in the expression for the entropy functional $\mathcal{H}$ in Lemma 5.3.4. We shall first show that

$$\int_0^T \psi_{p+1}(0,t) \int_0^\infty a_p(\tau,t)m_p(\tau,t)\ d\tau \times \int_0^\infty \left(\frac{n_p^k(\tau,t)}{m_p(\tau,t)}\right)^2\ d\mu_t^p(\tau)\ dt \tag{5.4.2}$$

$$\to \int_0^T \psi_{p+1}(0,t) \int_0^\infty a_p(\tau,t)m_p(\tau,t)\ d\tau \times \int_0^\infty \left(\frac{n_p^0(\tau,t)}{m_p(\tau,t)}\right)^2\ d\mu_t^p(\tau)\ dt$$

as $k \to \infty$, where $d\mu_t^p(\tau)$ is defined as in Lemma 5.3.4. Using the definition or $d\mu_t^p(\tau)$, we find that the above convergence is equivalently stated as:

$$\left|\int_0^T \int_0^\infty \left\{ \left(\frac{n_p^k(\tau,t)}{m_p(\tau,t)}\right)^2 - \left(\frac{n_p^0(\tau,t)}{m_p(\tau,t)}\right)^2 \right\} \psi_{p+1}(0,t) a_p(\tau,t) m_p(\tau,t) \ d\tau \ dt\right| \to 0,$$

as $k \to \infty$, with $a_p(\tau,t)$ defined as in Lemma 5.3.4. Now, we know that

$$\begin{aligned}&\left|\int_0^T \int_0^\infty \left\{ \left(\frac{n_p^k(\tau,t)}{m_p(\tau,t)}\right)^2 - \left(\frac{n_p^0(\tau,t)}{m_p(\tau,t)}\right)^2 \right\} \psi_{p+1}(0,t) a_p(\tau,t) m_p(\tau,t) \ d\tau \ dt\right| \\ \leq &\int_0^T \int_0^\infty \left| \left(\frac{n_p^k(\tau,t)}{m_p(\tau,t)}\right)^2 - \left(\frac{n_p^0(\tau,t)}{m_p(\tau,t)}\right)^2 \right| \psi_{p+1}(0,t) a_p(\tau,t) m_p(\tau,t) \ d\tau \ dt.\end{aligned} \tag{5.4.3}$$

We can factorise the difference of squares in the above integral as follows:

$$\left| \left(\frac{n_p^k(\tau,t)}{m_p(\tau,t)}\right)^2 - \left(\frac{n_p^0(\tau,t)}{m_p(\tau,t)}\right)^2 \right| = \left|\frac{n_p^k(\tau,t)}{m_p(\tau,t)} + \frac{n_p^0(\tau,t)}{m_p(\tau,t)}\right| \left|\frac{n_p^k(\tau,t)}{m_p(\tau,t)} - \frac{n_p^0(\tau,t)}{m_p(\tau,t)}\right|,$$

and by the fact that $n_p^k(\tau,t)$ and $n_p^0(\tau,t)$ are bounded by a constant multiple of $m_p(\tau,t)$ we find that

$$\left| \left(\frac{n_p^k(\tau,t)}{m_p(\tau,t)}\right)^2 - \left(\frac{n_p^0(\tau,t)}{m_p(\tau,t)}\right)^2 \right| \leq M \frac{|n_p^k(\tau,t) - n_p^0(\tau,t)|}{m_p(\tau,t)},$$

for some constant M. Substituting this into Equation (5.4.3) and cancelling out the $m_p(\tau,t)$ in the numerator and denominator gives,

$$\begin{aligned}&\left|\int_0^T \int_0^\infty \left\{ \left(\frac{n_p^k(\tau,t)}{m_p(\tau,t)}\right)^2 - \left(\frac{n_p^0(\tau,t)}{m_p(\tau,t)}\right)^2 \right\} \psi_{p+1}(0,t) a_p(\tau,t) m_p(\tau,t) \ d\tau \ dt\right| \\ \leq &M \int_0^T \int_0^\infty |n_p^k(\tau,t) - n^0(\tau,t)| \psi_{p+1}(0,t) a_p(\tau,t) \ d\tau \ dt.\end{aligned}$$

By the assumptions made for the problem P and the specification of the dual problem P^*, we find that $\psi_{p+1}(0,t)a_p(\tau,t) \in L^\infty([0,\infty) \times [0,T])$. Therefore, by the last convergence result of Lemma 5.4.1, we find that

$$M \int_0^T \int_0^\infty |n_i^k(\tau,t) - n^0(\tau,t)| \psi_{p+1}(0,t) a_p(\tau,t) \ d\tau \ dt \to 0$$

as $k \to \infty$. Thus, we have shown that Equation (5.4.2) holds.

We shall now show that

$$\begin{aligned}&\int_0^T \psi_{p+1}(0,t) \int_0^\infty a_p(\tau,t) m_p(\tau,t) \ d\tau \times \left(\int_0^\infty \frac{n_p^k(\tau,t)}{m_p(y,t)} d\mu_t^p(\tau)\right)^2 \ dt \\ \to &\int_0^T \psi_{p+1}(0,t) \int_0^\infty a_p(\tau,t) m_p(\tau,t) \ d\tau \times \left(\int_0^\infty \frac{n_p^0(\tau,t)}{m_p(y,t)} d\mu_t^p(\tau)\right)^2 \ dt\end{aligned} \tag{5.4.4}$$

as $k \to \infty$. Now, we know that

$$\left(\int_0^\infty \frac{n_p^k(\tau,t)}{m_p(\tau,t)}\,d\mu_t^p(\tau)\right)^2 - \left(\int_0^\infty \frac{n_p^0(\tau,t)}{m_p(\tau,t)}\,d\mu_t^p(\tau)\right)^2$$
$$= \left(\int_0^\infty \frac{n_p^k(\tau,t)}{m_p(\tau,t)} + \frac{n_p^0(\tau,t)}{m_p(\tau,t)}\,d\mu_t^p(\tau)\right)\left(\int_0^\infty \frac{n_p^k(\tau,t)}{m_p(\tau,t)} - \frac{n_p^0(\tau,t)}{m_p(\tau,t)}\,d\mu_t^p(\tau)\right).$$

The fact that $n_p^k(\tau,t)$ and $n_p^0(\tau,t)$ are bounded by a constant multiple of $m_p(\tau,t)$ implies that

$$\left(\int_0^\infty \frac{n_p^k(\tau,t)}{m_p(\tau,t)} + \frac{n_p^0(\tau,t)}{m_p(\tau,t)}\,d\mu_t^p(\tau)\right) \le M$$

for some constant $M > 0$. Using this fact we find that

$$\left|\int_0^T \psi_{p+1}(0,t)\int_0^\infty a_p(\tau,t)m_p(\tau,t)\,d\tau\left\{\left(\int_0^\infty \frac{n_p^k(\tau,t)}{m_p(y,t)}d\mu_t^p(\tau)\right)^2 - \left(\int_0^\infty \frac{n_p^0(\tau,t)}{m_p(y,t)}d\mu_t^p(\tau)\right)^2\right\}\,dt\right|$$
$$\le M\int_0^T \psi_{p+1}(0,t)\int_0^\infty a_p(\tau,t)m_p(\tau,t)\,d\tau \times \int_0^\infty \left|\frac{n_p^k(\tau,t)}{m_p(\tau,t)} - \frac{n_p^0(\tau,t)}{m_p(\tau,t)}\right|\,d\mu_t^p(\tau)\,dt.$$

Using the definition of $d\mu_t^p(\tau)$, we find that

$$M\int_0^T \psi_{p+1}(0,t)\int_0^\infty a_p(\tau,t)m_p(\tau,t)\,d\tau \times \int_0^\infty \left|\frac{n_p^k(\tau,t)}{m_p(\tau,t)} - \frac{n_p^0(\tau,t)}{m_p(\tau,t)}\right|\,d\mu_t^p(\tau)\,dt$$
$$\le M\int_0^T\int_0^\infty |n_p^k(\tau,t) - n_p^0(\tau,t)|\psi_{p+1}(0,t)a_p(\tau,t)\,d\tau\,dt.$$

By the last convergence result of Lemma 5.4.1 and the fact that $\psi_{p+1}(0,t)a_p(\tau,t) \in L^\infty([0,\infty)\times[0,T])$, we find that the right hand side of the above inequality tends to zero as $k \to \infty$. Therefore Equation (5.4.4) holds.

From Equations (5.4.2) and (5.4.4) we find that when the convex function $H(x)$ in the functional $\mathcal{H}$ is chosen such that $H(x) = x^2$, we obtain

$$\int_0^T \mathcal{H}_t(n^k|m,\psi)(t)\,dt \to \int_0^T \mathcal{H}_t(n^0|m,\psi)(t)\,dt,$$

as $k \to \infty$, where $\mathcal{H}$ is defined by Equation 5.3.8.

But since $\mathcal{H}$ is non-negative and $\mathcal{H}_t$ is non-positive, $\mathcal{H}$ must converge to some value as $t \to \infty$. Therefore, taking t_k the subsequence of times associated with the convergent sequence $n^k(\tau,t)$, we find that

$$\int_{t_k}^{t_k+T} \mathcal{H}_t(n|m,\psi)(t)\,dt \to 0,$$

as $k \to \infty$. However, from the way we constructed the sequence of times t_k in Lemma 5.4.1, it can be seen that the difference between t_{k+1} and t_k is a constant multiple of T_0, the period of ψ and m. But then

$$\int_{t_k}^{t_k+T} \mathcal{H}_t(n|m,\psi)(t)\,dt = \int_0^T \mathcal{H}_t(n^k|m,\psi)(t)\,dt$$

for all $k \geq 1$.

Consequently we see that $\int_0^T \mathcal{H}_t(n^k|m,\psi)(t)\ dt \to 0$ as $k \to \infty$. We thus have

$$\int_0^T \mathcal{H}_t(n^0|m,\psi)(t)\ dt = \lim_{k\to\infty} \int_0^T \mathcal{H}_t(n^k|m,\psi)(t)\ dt = 0.$$

Moreover, because $\mathcal{H}_t(n^0|m,\psi)(t) \leq 0$ for all $0 \leq t \leq T$, we find that

$$\mathcal{H}_t(n^0|m,\psi)(t) = 0, \qquad \text{a.e.} 0 \leq t \leq T.$$

The assumption that $m(\tau,t)$ and $\psi(\tau,t)$ are strictly positive (made at the beginning of this section) implies that

$$\psi_{p+1}(0,t) \int_0^\infty a_p(\tau,t) m_p(\tau,t)\ d\tau = \psi_{p+1}(0,t) m_{p+1}(0,t) > 0,$$

for all $p \in \{G_1, S, G_2\}$ and $t \geq 0$. The fact that $\mathcal{H}_t(n^0|m,\psi) = 0$ then implies that the equality condition of Jensen's inequality is satisfied; that is,

$$\left(\int_0^\infty \frac{n_p^0(\tau,t)}{m_p(\tau,t)}\ d\mu_t^p(\tau) \right)^2 = \int_0^\infty \left(\frac{n_p^0(\tau,t)}{m_p(\tau,t)} \right)^2\ d\mu_t^p(\tau), \qquad 0 \leq t \leq T,$$

for all $p \in \{G_1, S, G_2\}$. Since $H(x) = x^2$ has a strictly positive double-derivative, the equality condition is only satisfied when $n_p^0(\tau) = \theta_p(t) m_p(\tau,t)$ (see Appendix C) except on a set of zero μ_t^p-measure for all $0 \leq t \leq T$. That is, $n_p^0(\tau,t) = \theta_p(t) m_p(\tau,t)$ (almost everywhere) on the support of $a_p(\cdot,t)$ for each $0 \leq t \leq T$. (where the functions a_p are defined as in Lemma 5.3.4). But, by the assumption made in the statement of problem P that $k_p(\tau,t)$ is strictly positive for all $p \in \{G_1, S, G_2\}$, we find that $a_p(\tau,t)$ is strictly positive. Therefore $n_p^0(\tau,t) = \theta_p(t) m_p(\tau,t)$ for almost every $(\tau,t) \in [0,\infty) \times [0,T]$. $\square$

We now show that the functions $\theta_p(t)$ must all be constant and equal to each other, which implies that $n^0(\tau,t)$ is a constant multiple of $m(\tau,t)$.

Theorem 5.4.3. *Take the sequence $n^k(\tau,t)$ from Lemma 5.4.2 with limit function $n^0(\tau,t)$ such that $n_p^0(\tau,t) = \theta_p(t) m_p(\tau,t)$ for all $p = \{G_1, S, G_2\}$. We find that $\theta_p(t) = K$ for some constant K on $0 \leq t \leq T$ for $p \in \{G_1, S, G_2\}$.*

Proof. Let $n^0(\tau,0) = g(\tau)$, then defining

$$\begin{aligned} b_{G_1}(\tau,t) &= k_{G_1}(\tau,t) + \mu_{G_1}(\tau,t), \\ b_S(\tau,t) &= k_S(\tau,t) + \mu_S(\tau,t), \\ b_{G_2}(\tau,t) &= k_{G_2}(\tau,t) + \mu_{G_2}(\tau,t), \end{aligned}$$

the solution of each compartment n_p^0, $p \in \{G_1, S, G_2\}$, is found to be

$$n_p^0(\tau,t) = \begin{cases} \theta_{p-1}(t-\tau) m_p(0,t-\tau) \exp\left(-\int_0^\tau b_p(s,s+t-\tau)\ ds\right), & 0 \le \tau < t < T, \\ g_p(\tau - t) \exp\left(-\int_{\tau-t}^{\tau} b_p(s,s+t-\tau)\ ds\right), & t \le \tau. \end{cases} \tag{5.4.5}$$

This is shown in the following way:

Let $n^k(\tau,0) = g^k(\tau)$ for $k = 1, 2, \ldots$. Then solving problem P along the characteristic curves, we find the following solution for each compartment, n_p^k, of n^k.

$$n_p^k(\tau,t) = \begin{cases} n_p^k(0,t-\tau) \exp\left(-\int_0^\tau b_p(s,s+t-\tau)\ ds\right), & \tau < t < T, \\ g_p^k(\tau - t) \exp\left(-\int_{\tau-t}^{\tau} b_p(s,s+t-\tau)\ ds\right), & t \le \tau. \end{cases}$$

Now, from Lemma 5.4.1, we see that

$$\int_0^T \int_0^\infty |n_p^k(\tau,t) - n_p^l(\tau,t)|\ d\tau dt \to 0, \qquad k, l \to \infty.$$

But the above integral is equal to

$$\begin{aligned} &\int_0^T \int_0^t |n_p^k(0,t-\tau) - n_p^l(0,t-\tau)| \exp\left(-\int_0^\tau b_p(s,s+t-\tau)\ ds\right)\ d\tau dt \\ +&\int_0^T \int_t^\infty |g_p^k(\tau-t) - g_p^l(\tau-t)| \exp\left(-\int_{\tau-t}^{\tau} b_p(s,s+t-\tau)\ ds\right)\ d\tau dt. \end{aligned} \tag{5.4.6}$$

The fact that expression (5.4.6) tends to zero as $k, l \to \infty$ implies that

$$g_p^k(\tau) \to g_p^*(\tau), \qquad k \to \infty,\ (\text{in } L^1_{loc}[0,\infty)) \tag{5.4.7}$$

$$n_p^k(0,t) \to n_p^*(0,t), \qquad k \to \infty,\ (\text{in } L^1[0,T]), \tag{5.4.8}$$

for some limit functions $g_p^*(\tau)$ and $n_p^*(0,t)$, $p = \{G_1, S, G_2\}$. Note that since n is bounded by a constant multiple of m, we have $g_p^k(\tau)$ bounded by a constant multiple of $m_p(\tau,0)$ and, consequently, $g_0^*(\tau)$ is also bounded by a constant multiple of $m_p(\tau,0)$. Thus, it can be shown that the sequence $n_p^k(\tau,t)$ converges in $L^1_{loc}([0,\infty) \times [0,T])$ to

$$n_p^*(\tau,t) = \begin{cases} n_p^*(0,t-\tau) \exp\left(-\int_0^\tau b_p(s,s+t-\tau)\ ds\right), & 0 \le \tau < t < T, \\ g_p^*(\tau - t) \exp\left(-\int_{\tau-t}^{\tau} b_p(s,s+t-\tau)\ ds\right), & t \le \tau. \end{cases} \tag{5.4.9}$$

But from Lemma 5.4.1, we know that $n_p^0(\tau,t)$ is the limit of $n_p^k(\tau,t)$ in $L^1_{loc}([0,\infty) \times [0,T])$. Therefore $n_p^*(\tau,t) = n_p^0(\tau,t)$ (almost everywhere) for all $p = \{G_1, S, G_2\}$ and it only remains to find $n^*(0,t)$. Using Lemma 5.4.1 again, we find that

$$\int_0^T \int_0^\infty |n_p^k(\tau,t) - n_p^0(\tau,t)| a_p(\tau,t)\ d\tau dt \to 0, \qquad k \to \infty,$$

where $a_p(\tau,t)$, $p \in \{G_1, S, G_2\}$, is defined as in Lemma 5.3.4 (note that $a_p(\tau,t) \in L^\infty([0,\infty) \times [0,T])$ for $p \in \{G_1, S, G_2\}$). But the above expression is greater than or equal to

$$\int_0^T \left| n_{p+1}^k(0,t) - \theta_p(t) \int_0^\infty m_p(\tau,t) a_p(\tau,t)\, d\tau \right| \, dt. \tag{5.4.10}$$

The expression (5.4.10), in turn, is equal to

$$\int_0^T |n_{p+1}^k(0,t) - \theta_p(t) m_{p+1}(0,t)| \, dt,$$

which, by Equation (5.4.8), reduces in the limit as $k \to \infty$ to $||n_{p+1}^*(0,t) - \theta_p(t) m_{p+1}(0,t)||_{L^1[0,T]}$. We have thus found that

$$||n_{p+1}^*(0,t) - \theta_p(t) m_{p+1}(0,t)||_{L^1[0,T]} = 0,$$

for $p \in \{G_1, S, G_2\}$. This implies that $n_p^*(0,t) = \theta_{p-1}(t) m_p(0,t)$ which, from Equation (5.4.9) and the equivalence of $n^*(\tau,t)$ and $n^0(\tau,t)$, gives us Equation (5.4.5) as desired.

Taking the solution $n^0(\tau,t)$, as given in (5.4.5), it can be seen that

$$\begin{aligned} n_p^0(\tau,t) &= \theta_{p-1}(t-\tau) m_p(0,t-\tau) \exp\left(-\int_0^\tau b_p(s, s+t-\tau)\, d\tau \right) \\ &= \theta_{p-1}(t-\tau) m_p(\tau,t), \qquad \tau < t \le T. \end{aligned}$$

But it is already known that $n_p^0(\tau,t) = \theta_p(t) m_p(\tau,t)$ for $0 \le t \le T$; thus we have the following result:

$$\theta_{p-1}(t-\tau) = \theta_p(t), \qquad \tau < t \le T. \tag{5.4.11}$$

Therefore iterating (5.4.11), we find $\theta_p(t-3\tau) = \theta_p(t)$ for all $3\tau < t \le T$. Substituting τ for 3τ then gives

$$\theta_p(t-\tau) = \theta_p(t) \qquad \tau < t \le T,$$

for all $p \in \{G_1, S, G_2\}$. We therefore find that $\theta_p(t) = \theta_p$ is constant for $0 \le t \le T$. Moreover by (5.4.11) we find that $\theta_{G_1} = \theta_S = \theta_{G_2}$. Let K be the common value of the constants θ_p, $p \in \{G_1, S, G_2\}$. Then from the above it may be said that $n^0(\tau,t) = Km(\tau,t)$ when $0 \le t \le T$. □

The above results have shown us that given a sequence of time windows $t_k \le t \le t_k + T$, we may pick a subsequence such that $n(\tau,t)$ converges in some sense to the limit function $Km(\tau,t)$. We now take the convergence which occurs in a sequence of time windows and use Equation (5.3.4) from Lemma 5.3.3 to show that this convergence happens as $t \to \infty$. Thus we move from a discrete picture of the behaviour of the solution n to a more continuous picture. Finally we use Equation (5.3.3) to find an expression for the constant K in terms of the initial conditions $n_0(\tau)$ for n.

Theorem 5.4.4. *Let $n(\tau,t)$, $m(\tau,t)$ and $\psi(\tau,t)$ be defined as in the beginning of this section, with n bounded by a constant multiple of m for all $t \geq 0$. Let*

$$K^* = \int_0^\infty \psi^T(\tau,0)n_0(\tau)\ d\tau.$$

Then

$$\int_0^\infty \psi^T(\tau,t)|n(\tau,t) - K^*m(\tau,t)|\ d\tau \to 0 \tag{5.4.12}$$

as $t \to \infty$.

Proof. It has been shown in Theorem 5.4.3 that

$$n_p^k(\tau,t) \to n_p^0(\tau,t) = Km_p(\tau,t)$$

in $L^1_{loc}([0,\infty)\times[0,\infty))$ as $k \to \infty$ for all $p \in \{G_1, S, G_2\}$ and some constant K.

Now, consider the expression

$$\int_0^T \int_0^\infty \psi^T(\tau,t)|n^k(\tau,t) - Km(\tau,t)|\ d\tau = \sum_p \int_0^T \int_0^\infty \psi_p(\tau,t)\left|n_p^k(\tau,t) - Km_p(\tau,t)\right|\ d\tau.$$

Using Lemma 5.4.1 and the fact that $\psi_p(\tau,t) \in L^\infty([0,\infty)\times[0,T])$ gives

$$\int_0^T \int_0^\infty \psi^T(\tau,t)|n^k(\tau,t) - Km(\tau,t)|\ d\tau \to 0 \tag{5.4.13}$$

as $k \to \infty$.

From Lemma 5.3.3, Equation (5.3.4), we know that the quantity

$$\int_0^\infty \psi^T(\tau,t)|n(\tau,t) - Km(\tau,t)|\ d\tau$$

is non-increasing. Moreover, it is a non-negative quantity and therefore tends to some limit $\varepsilon \geq 0$. Equation (5.4.13) implies that $\varepsilon = 0$. It now remains to be seen whether $K = K^*$.

To show that $K = K^*$, consider that

$$\left|\int_0^\infty \psi^T(\tau,t)n(\tau,t) - K\psi^T(\tau,t)m(\tau,t)\ d\tau\right| \leq \int_0^\infty \psi^T(\tau,t)|n(\tau,t) - Km(\tau,t)|\ d\tau$$

Therefore

$$\left|\int_0^\infty \psi^T(\tau,t)n(\tau,t) - K\psi^T(\tau,t)m(\tau,t)\ d\tau\right| \to 0$$

as $t \to \infty$. But

$$\left|\int_0^\infty \psi^T(\tau,t)n(\tau,t) - K\psi^T(\tau,t)m(\tau,t)\ d\tau\right| = |K^* - K|,$$

where K^* is defined in the statement of this theorem. Therefore $K = K^*$ and the desired result has been proved. ∎

We now drop the requirement that $n(\tau,t)$ is bounded by a constant multiple of $m(\tau,t)$ to obtain the theorem which has been the aim of this section:

Theorem 5.4.5. *Let $n(\tau,t)$, $m(\tau,t)$ and $\psi(\tau,t)$ be defined as in the beginning of this section, but this time drop the assumption that n is bounded by a constant multiple of m. Let $\psi(\tau,t)$ be scaled such that*

$$\int_0^\infty \psi^T(\tau,t)m(\tau,t)\ d\tau = 1,$$

for all $t \geq 0$ and, as before, let

$$K^* = \int_0^\infty \psi^T(\tau)n_0(\tau)\ d\tau.$$

Then

$$\int_0^\infty \psi^T(\tau,t)|n(\tau,t) - K^*m(\tau,t)|\ d\tau \to 0 \tag{5.4.14}$$

as $t \to \infty$.

Proof. We assumed at the beginning of this section that $m(\tau,t)$ was positive. Thus, as in Theorem 3.3.4, Chapter 3, we can split $n_0(\tau)$ into 'unbounded' and 'bounded' parts $n_u(\tau)$ and $n_b(\tau)$, which we define as follows:

$$n_u(\tau) = n_0(\tau) - n_b(\tau); \qquad n_b(\tau) = \begin{cases} n_0(\tau), & \tau < \tau_0, \\ 0, & \tau \geq \tau_0, \end{cases}$$

for some $\tau_0 > 0$. Let us denote by $n_u(\tau,t)$ and $n_b(\tau,t)$ the solutions of problem P corresponding to the initial conditions $n_u(\tau)$ and $n_b(\tau)$.

Now, since n_b has compact support and $m_0(\tau) = m(\tau,0) > 0$, we find that $n_b(\tau) \leq Cm_0(\tau)$ for some constant C. Thus, Theorem 5.4.4 applies to the solution $n_b(\tau,t)$ of problem P arising from the initial conditions $n_b(\tau)$.

Define

$$K^b = \int_0^\infty \psi^T(\tau,t)n_b(\tau,t)\ d\tau.$$

Note that for any $\varepsilon > 0$ we may choose τ_0 (in the definition of $n_b(\tau)$) large enough such that

$$0 \leq K^* - K^b = \int_0^\infty \psi^T(\tau,0)n_u(\tau)\ d\tau < \varepsilon.$$

With this in mind, we note that

$$\begin{aligned}\int_0^\infty \psi^T(\tau,t)|n(\tau,t) - K^*m(\tau,t)|\ d\tau \leq &\int_0^\infty \psi^T(\tau,t)|n_b(\tau,t) - K^bm(\tau,t)|\ d\tau \\ &+ \int_0^\infty \psi^T(\tau,t)|n_u(\tau,t)|\ d\tau \\ &+ \int_0^\infty \psi^T(\tau,t)(K^* - K^b)|m(\tau,t)|\ d\tau.\end{aligned}$$

Thus, for any $\varepsilon > 0$ we may choose τ_0 large enough such that

$$\int_0^\infty \psi^T(\tau,t)|n(\tau,t) - K^* m(\tau,t)|\ d\tau \leq \int_0^\infty \psi^T(\tau,t)|n_b(\tau,t) - K^b m(\tau,t)|\ d\tau + \varepsilon.$$

Taking the limit of the above inequality as $t \to \infty$ gives

$$\lim_{t\to\infty} \int_0^\infty \psi^T(\tau,t)|n(\tau,t) - K^* m(\tau,t)|\ d\tau \leq \varepsilon$$

for any $\varepsilon > 0$. Thus we find that Equation (5.4.14), in the statement of the theorem, must hold. $\square$

The steps followed in the proof of Theorem 5.4.4 (see the overview of the proof at the beginning of this section) is an expanded argument similar to the proof of Theorem 5.2, [49]. Here, however, care has been taken in making sure that, in the evaluation of $\mathcal{H}_t$, the derivative operator could be taken inside the integral, and we make sure that $\mathcal{H}$ exists by assuming that n is bounded by a constant multiple of m until the last result (Theorem 5.4.5) of this section. Also, in [49] it is suggested to use $H(x) = |x|$ in the entropy functional $\mathcal{H}$. However, this is not a strictly convex function and so using $H(x) = |x|$ will not allow the use of Jensen's inequality to show that $n^0(\tau,t) = Km(\tau,t)$. The fact that we have to use a strictly convex function means that weak compactness (used in [49]) of the sequence $n^k(\tau,t)$ is not enough to show that

$$\lim_{k\to\infty} \int_0^T \mathcal{H}(n^k|m,\psi)(t)\ dt \to \int_0^T \mathcal{H}(n^0|m,\psi)(t)\ dt.$$

In fact, if we had used $H(x) = |x|$ in the present situation, we would always have $\mathcal{H}(n|m,\psi)(t) = 0$, regardless of whether n/m were constant or not. But it is an essential feature of the proof that we obtain n/m is constant when $\mathcal{H}(n|m,\psi)(t) = 0$. In summary, the analysis required is more complicated than the impression given in [49]. A final point of difference is that the analysis here has been carried out for a multi-compartment model.

5.5 Existence of steady age-distributions given time-independent coefficients

Here we apply the results from Section 5.4 to show that steady age-distributions $N(\tau)$ exist and are stable when D_{out} and D_{in} are functions of τ only. We find in Theorem 5.5.4 that given any initial conditions in $(L^1 \cap L^\infty)[0,\infty)$, the shape of the solution $n(\tau,t)$ to problem P will tend to $N(\tau)$.

We shall work with the modified problems $P(\lambda)$ and $P^*(\lambda)$, defined as follows:

Definition 5.5.1. *Let $\lambda \in \mathbb{R}$. Define problem $P(\lambda)$ as the new problem obtained by replacing D_{out} with $D_{out} + \lambda I$ in problem P. Likewise let problem $P^*(\lambda)$ denote the new problem formed by replacing D_{out} with $D_{out} + \lambda I$ in problem P^*.*

Thus, any solution, $n(\tau, t)$ of problem $P(\lambda)$ satisfies

$$n_t(\tau, t) + n_\tau(\tau, t) = -(D_{out}(\tau, t) + \lambda I)n(\tau, t)$$

and any solution, $\psi(\tau, t)$ of problem $P^*(\lambda)$ satisfies

$$\psi_t(\tau, t) + \psi_\tau(\tau, t) - (D_{out}(\tau, t) + \lambda I)\psi(\tau, t) + D_{in}^T(\tau, t)\psi(0, t) = 0.$$

Note that if $n(\tau, t)$ is a solution to problem $P(\lambda)$, then $n(\tau, t)e^{\lambda t}$ is a solution of problem P. Likewise if $\psi(\tau, t)$ is a solution to problem $P^*(\lambda)$, then $\psi(\tau, t)e^{-\lambda t}$ is a solution of problem P^*.

We first find stationary solutions to the modified problems $P(\lambda)$ and $P^*(\lambda)$, for some $\lambda \in \mathbb{R}$. That is, we find solutions $n(\tau, t)$ and $\psi(\tau, t)$ to problem $P(\lambda)$ and $P^*(\lambda)$ that are independent of time. It is shown that when there exists a λ_0 such that $P(\lambda_0)$ and $P^*(\lambda_0)$ have stationary solutions, then any (non-stationary) solution to $P(\lambda_0)$ will tend to the steady-state solution as $t \to \infty$. This implies that the shape of the age-distributions in each phase of the solution to P will always tend to the shape described by the stationary solution of $P(\lambda_0)$, with the overall number of cells tending to $Ce^{\lambda_0 t}$ as $t \to \infty$ for some constant C. Sufficient conditions are given for λ_0 to exist. Note that by finding stationary solutions to problem $P(\lambda)$, we are finding solutions to problem P of the form

$$n(\tau, t) = e^{\lambda t}N(\tau),$$

and therefore $N(\tau)$ is a steady age-distribution of problem P, since the age-distribution of cells, $n(\tau, t)$, retains the same shape $N(\tau)$, while the overall number of cells may be growing or decaying.

An alternative approach to that taken here, in the case with time-independent coefficients, is to concentrate on the boundary at $\tau = 0$. Here we can obtain a Volterra integral equation of the second kind and attempt to analyse its asymptotic behaviour. This was done in [52] for a one compartment model using the theory of renewal equations from [12]. The case for multiple compartments, which gives a system of renewal equations, is more complicated (see chapter 8 of [12]). Presently, we approach this problem using the theory from Section 5.4 as a relatively simple example application, before moving on to the case where the birth and death terms of problem P are periodic in time.

Lemma 5.5.2. *Let $P(\lambda)$ (resp. $P^*(\lambda)$) be defined as above. Let $\mathcal{M} > 0$ be the infimum of $k_p(\tau, t) + \mu_p(\tau, t)$ over all $p \in \{G_1, S, G_2\}$ and $(\tau, t) \in [0, \infty) \times [0, \infty)$. This exists due to the assumptions made in the statement of problem P.*

The results of Sections 5.2, 5.3 and 5.4 still hold when applied to problems $P(\lambda)$ and $P^*(\lambda)$ for all $\lambda > -\mathcal{M}$.

Proof. If we let $\mu_p'(\tau,t) = \mu_p(\tau,t) + \lambda$, $p \in \{G_1, S, G_2\}$, then problem $P(\lambda)$ is merely an instance of problem P with $\mu_p(\tau,t)$ replaced by $\mu_p'(\tau,t)$. It may be the case that $\mu_p(\tau,t) < 0$ at some point for some or all $p \in \{G_1, S, G_2\}$, which represents a negative death rate (this is not realistic biologically, but mathematically presents no problem), but due to our choice of $\lambda > -\mathcal{M}$, all of the assumptions required by problem P are satisfied by problem $P(\lambda)$. Moreover, problem $P^*(\lambda)$ is the dual problem to problem $P(\lambda)$ in the same way that P^* is the dual problem to problem P see the beginning of Section 5.3).

Therefore the results of Sections 5.2, 5.3 and 5.4 all hold for problem $P(\lambda)$ and $P^*(\lambda)$. $\square$

For the remainder of this section it is assumed that k_p and μ_p, $p \in \{G_1, S, G_2\}$ are functions of τ only and are independent of time.

Let $a_p(\tau)$ be defined as in Lemma 5.3.4:

$$a_{G_1}(\tau) = k_{G_1}(\tau); \qquad a_S(\tau) = k_S(\tau); \qquad a_{G_2}(\tau) = 2k_{G_2}(\tau),$$

and let

$$b_{G_1}(\tau) = k_{G_1}(\tau) + \mu_{G_1}(\tau); \qquad b_S(\tau) = k_S(\tau) + \mu_S(\tau); \qquad b_{G_2}(\tau) = k_{G_2}(\tau) + \mu_{G_2}(\tau).$$

Define the term

$$Q(\lambda) = \prod_p \int_0^\infty a_p(s) \exp\left(- \int_0^s b_p(\xi) + \lambda \, d\xi \right) \, ds.$$

Then we have the following result.

Theorem 5.5.3. *Let $\mathcal{M} > 0$ be the infimum of $k_p(\tau,t) + \mu_p(\tau,t)$ over all $p \in \{G_1, S, G_2\}$ and $(\tau,t) \in [0,\infty) \times [0,\infty)$. (This exists due to the assumptions made in the statement of problem P.) Assume that $Q(\kappa) \geq 1$ for some $\kappa > -\mathcal{M}$. Then there exists some triple (λ_0, N, Ψ) such that $\lambda_0 \geq \kappa$, $N(\cdot) \in (L^1 \cap L^\infty)[0,\infty)$ is a strictly positive stationary solution to $P(\lambda_0)$ and $\Psi(\cdot) \in L^\infty[0,\infty)$ is a strictly positive stationary solution of $P^*(\lambda_0)$.*

Proof. The solution of $N(\tau)$ must be of the form

$$N_p(\tau) = N_p(0) \exp\left(- \int_0^\tau b_p(s) + \lambda \, ds \right),$$

with

$$N_p(0) = \int_0^\infty a_{p-1}(\tau) N_{p-1}(\tau) \, d\tau,$$

for all $p \in \{G_1, S, G_2\}$. This gives rise to the necessary and sufficient condition for a solution N to exist:

$$
\begin{aligned}
N_{G_1}(0) &= \int_0^\infty a_{G_2}(s) N_{G_2}(s)\, ds && (5.5.1)\\
&= \int_0^\infty a_{G_2}(s) \left[\int_0^\infty a_S(\xi) N_S(\xi)\, d\xi\right] \exp\left(-\int_0^s b_{G_2}(\xi) + \lambda\, d\xi\right)\, ds\\
&= \int_0^\infty a_S(s) N_S(s)\, ds \times \left[\int_0^\infty a_{G_2}(s) \exp\left(-\int_0^s b_{G_2}(\xi) + \lambda\, d\xi\right)\, ds\right]\\
&\vdots\\
1 &= \prod_p \int_0^\infty a_p(s) \exp\left(-\int_0^s b_p(\xi) + \lambda\, d\xi\right)\, ds && (5.5.2)
\end{aligned}
$$

Equation (5.5.2) can be expressed as the requirement that $Q(\lambda) = 1$. By assumption we have $Q(\kappa) > 1$. Moreover $Q(\lambda)$ varies continuously with λ when $\lambda > -\mathcal{M}$ with $Q(\lambda) \to 0$ as $\lambda \to \infty$. Thus, by the intermediate value theorem, there exists some $\lambda_0 \geq \kappa$ such that a stationary solution N exists to the problem $P(\lambda_0)$, with ratios between $N_p(0)$ given by:

$$N_{p+1}(0) = N_p(0) \int_0^\infty a_p(s) \exp\left(-\int_0^s b_p(\xi) + \lambda_0\, d\xi\right)\, ds.$$

The ratios between the values $N_p(0)$ are positive. Thus we choose $N_{G_1}(0)$ positive so as to produce a positive overall solution $N(\tau)$.

A solution Ψ then exists to the problem $P^*(\lambda_0)$ as long as $\Psi_p(0)$ can be found for all $p \in \{G_1, S, G_2\}$ such that

$$\Psi_p(\tau) = e^{\int_0^\tau b_p(s) + \lambda_0\, ds} \left[\Psi_p(0) - \int_0^\tau a_p(s) \Psi_{p+1}(0) \exp\left(-\int_0^s b_p(\xi) + \lambda_0\ ,\, d\xi\right)\, ds\right] \qquad (5.5.3)$$

is non-negative (Equation (5.5.3) is obtained by solving the differential equation in (5.3.1) with $\psi_t(\tau, t) = 0$ and D_{out} replaced with $D_{out} + \lambda I$). We also desire a bounded solution $\Psi(\tau)$ and therefore take

$$\Psi_p(0) = \Psi_{p+1}(0) \int_0^\infty a_p(s) \exp\left(-\int_0^s b_p(\xi) + \lambda_0\, d\xi\right)\, ds. \qquad (5.5.4)$$

If we also take only positive values $\Psi_p(0)$, then $\Psi_p(\tau)$ is strictly positive, since

$$\int_0^\infty a_p(s) \exp\left(-\int_0^s b_p(\xi) + \lambda_0\, d\xi\right)\, ds > \int_0^\tau a_p(s) \exp\left(-\int_0^s b_p(\xi) + \lambda_0\, d\xi\right)\, ds, \qquad 0 \leq x < \infty.$$

(a_p, $p \in \{G_1, S, G_2\}$, is strictly positive due the assumption, made in the statement of problem P, that the functions k_p are strictly positive.) Iterating the above equation gives the requirement (5.5.2), which is satisfied due to the choice of λ which was made when searching for an eigenfunction N.

From the form of N we see that $N_p \in (L^1 \cap L^\infty)[0,\infty)$ for all $p \in \{G_1, S, G_2\}$.

Substituting $\Psi_p(0)$ from (5.5.4) into (5.5.3) and putting everything over a common denominator gives

$$\Psi_p(\tau) = \Psi_p(0)\frac{\int_\tau^\infty a_p(s)\exp\left(-\int_\tau^s b_p(\xi) + \lambda_0 \; d\xi\right) \; ds}{\int_0^\infty a_p(s)\exp\left(-\int_0^s b_p(\xi) + \lambda_0 \; d\xi\right) \; ds}$$

The integral in the denominator converges by virtue of the fact that $\lambda_0 > -\mathcal{M} \geq -b_p(\xi)$ for all $p \in \{G_1, S, G_2\}$. Consider now the numerator of the above expression. We have

$$\begin{aligned}\int_\tau^\infty a_p(s)\exp\left(-\int_\tau^s b_p(\xi) + \lambda_0 \; d\xi\right) \; ds &= \int_0^\infty a_p(s+\tau)\exp\left(-\int_0^s b_p(\xi+\tau) \; d\xi\right) e^{-\lambda_0 s} \; ds \\ &\leq \int_0^\infty ||a_p||_\infty e^{-(\mathcal{M}+\lambda_0)s} \; ds.\end{aligned}$$

Thus the numerator is bounded, and as a consequence, $\Psi_p \in L^\infty[0,\infty)$ for all $p \in \{1,2,3\}$. From the form of $\Psi_p(\tau)$ and Equation 5.5.4, we must have $\Psi_p(0) > 0$ for all $p \in \{G_1, S, G_2\}$ in order to obtain a non-trivial solution Ψ. □

We shall now prove some results regarding the stability of the steady-state solution N of problem $P(\lambda_0)$ using the theory from Section 5.4.

Theorem 5.5.4. *Let (λ_0, Ψ, N) be the triple from Theorem 5.5.3 with $\Psi(\tau)$ scaled such that*

$$\int_0^\infty \Psi^T(\tau)N(\tau) \; d\tau = 1.$$

This is possible since any constant multiple of a solution of $P^*(\lambda_0)$ is also a solution of $P^*(\lambda_0)$.

Let $n(\tau,t)$ be a solution to problem $P(\lambda_0)$, and let

$$K^* = \int_0^\infty \Psi^T(\tau)n_0(\tau) \; d\tau$$

Then

$$\int_0^\infty \Psi^T(\tau,t)|n(\tau,t) - K^*N(\tau)| \; d\tau \to 0 \tag{5.5.5}$$

as $t \to \infty$.

Proof. Note that $N(\tau)$ is strictly positive and that each component of $\Psi(0)$ is positive. Thus, we may apply Theorem 5.4.5 with $m(\tau,t) = N(\tau)$ and $\psi(\tau,t) = \Psi(\tau)$. □

Corollary 5.5.5. *Let $n(\tau,t)$ be a solution to problem P and let $\mathcal{M}$ be defined as in Theorem 5.5.3. Assume that $Q(\kappa) > 1$ for some $\kappa > -\mathcal{M}$ and let (λ_0, Ψ, N) and K^* be defined as above. Then*

$$\int_0^\infty \Psi^T(\tau)|n(\tau,t)e^{-\lambda_0 t} - K^*N(\tau)| \; d\tau \to 0.$$

as $t \to \infty$.

Proof. It is easily seen that $n(\tau, t)e^{-\lambda_0 t}$ is a solution to problem $P(\lambda_0)$. We may thus apply Theorem 5.5.4. $\square$

5.6 Existence of periodic attractors given periodic coefficients

Consider now problem P where the components k_p and μ_p, $p \in \{G_1, S, G_2\}$, of the matrices D_{out} and D_{in} are assumed to be dependent on time and T-periodic.

We first aim to prove the existence of periodic solutions to $P(\lambda)$ and $P^*(\lambda)$ for some value of λ. Similarly to [49], we express periodic solutions (defined for all $t \in \mathbb{R}$) in the form:

$$m(\tau, t) = \exp\left(-\int_0^\tau \lambda I + D_{out}(\xi, \xi + t - \tau)\, d\xi\right) \mathcal{N}(t - \tau), \tag{5.6.1}$$

$$\psi(\tau, t) = \int_\tau^\infty \exp\left(-\int_\tau^s \lambda I + D_{out}(\xi, \xi + t - \tau)\, d\xi\right) D_{in}^T(s, s + t - \tau)\mathcal{U}(s + t - \tau)ds \tag{5.6.2}$$

for some T-periodic functions $\mathcal{N}(t)$ and $\mathcal{U}(t)$ defined for all $t \in \mathbb{R}$. The above expressions for m and ψ are solutions to problems $P(\lambda)$ and $P^*(\lambda)$ when $\mathcal{N}(t) = m(0, t)$ and $\mathcal{U}(t) = \psi(0, t)$ for all $t \geq 0$. The solution above for $m(\tau, t)$ is a special case of Equation (5.2.1) when $m(0, t) = \mathcal{N}(t)$ is defined for all $t \in \mathbb{R}$.

The 'solution' (5.6.2) for $\psi(\tau, t)$ does not necessarily satisfy $\mathcal{U}(t) = \psi(0, t)$. However, the form of $\psi(\tau, t)$ above is derived by solving (5.3.1) along characteristic lines to yield:

$$\begin{aligned}\psi(\tau, t) = \exp\left(\int_0^t \lambda I + D_{out}(\tau - t + s, s)\, ds\right) \Bigg[C(\tau - t) - \\ \int_0^t \exp\left(-\int_0^s \lambda I + D_{out}(\tau - t + \xi, \xi)\, d\xi\right) D_{in}^T(\tau - t + s, s)\psi(0, s)ds \Bigg],\end{aligned}$$

for some unknown function C. We then choose

$$C(\tau - t) = \int_0^\infty \exp\left(-\int_0^s \lambda I + D_{out}(\tau - t + \xi, \xi)\, d\xi\right) D_{in}^T(\tau - t + s, s)\psi(0, s)ds,$$

with the aim of obtaining a bounded expression for $\psi(\tau, t)$. This gives the solution from (5.6.2) after a change of variables in the integral. If we consider $\lambda \geq 0$, this choice of $C(\tau - t)$ guarantees positivity and boundedness of the solution $\psi(\tau, t)$, as well as the periodicity of $\psi(0, t)$, although it is possible that this is not the only form that the solution for $\psi(\tau, t)$ could take. As long as we can find some periodic $\mathcal{U}(t)$ such that $\psi(0, t) = \mathcal{U}(t)$, then $\psi(\tau, t)$ will be a solution to the dual problem $P^*(\lambda)$.

Note that if $m(\tau, t)$ is a periodic solution of problem $P(\lambda)$, then

$$n(\tau, t) = e^{\lambda t} m(\tau, t),$$

is a solution of problem P. Thus, $n(\tau, t)$ has periodic behaviour superimposed with exponential growth or decay.

The proof of the existence of periodic solutions to problems $P(\lambda)$ and $P^*(\lambda)$ is handled similarly here to the one-compartment case, which was done in [49] (although the treatment there is quite brief). There, the problems $P(\lambda)$ and $P^*(\lambda)$ are reduced to integral equations for $m(0,t)$ and $\psi(0,t)$. The Krein-Rutman Theorem ([56] page 79) is then used to show that there exists a positive eigenvalue $\nu(\lambda)$ to the integral operators (with periodic eigenfunctions $m(0,t)$ and $\psi(0,t)$). Finally, it is claimed that for some $\lambda_0 \geq 0$, we have $\nu(\lambda_0) = 1$, which implies the existence of a solution to the integral equations.

We begin by giving a statement of the Krein-Rutman Theorem from [56]:

Definition 5.6.1. *A subset K of a Banach space $\mathcal{B}$ is called a proper convex cone if the following three conditions hold:*

1. *$x \in K$ implies $tx \in K$ for all $t \geq 0$;*

2. *$x, y \in K$ implies $x + y \in K$;*

3. *$0 \neq x \in K$ implies $-x \notin K$.*

Theorem 5.6.2 (Krein-Rutman)**.** *Let $\mathcal{B}$ be a Banach space and $K \subset \mathcal{B}$ be a closed proper convex cone with interior K_I and boundary ∂K. Let $A : \mathcal{B} \to \mathcal{B}$ be a compact operator with spectrum $\sigma(A)$, and let $\lambda_0 = \sup \Re(\sigma(A))$ denote the supremum of the real part of the spectrum of A. The following two results hold*

1. *Assume that $AK \subset K$ and that A has a non-zero point in its spectrum. Then $\lambda_0 > 0$, $\lambda_0 \in \sigma(A)$ and $|\lambda| \leq \lambda_0$ for all $\lambda \in \sigma(A)$. There exists an eigenvector $v \in K$ for λ_0.*

2. *Assume that $AK \subset K$ and that for all $0 \neq x \in \partial K$ there exists an $n > 0$ such that $A^n x \in K_I$. Then $\lambda_0 > 0$, $\lambda_0 \in \sigma(A)$ and $|\lambda| \leq \lambda_0$ for all $\lambda \in \sigma(A)$. The eigenvalue λ_0 is of multiplicity one and its eigenspace is generated by an element of K_I. The eigenvectors corresponding to eigenvalues in $\sigma(A) - \{\lambda_0\}$ are not in K.*

Note that the full theorem deals with the dual cone, K^*, of the cone K. We do not make any use of K^* and so do not state that part of the theorem. See [42] for the original work by Krein and Rutman.

Below we will be working with a set of functions, which we call $C_{per}[0,T]$, defined as follows:

Definition 5.6.3. *Let $C_{per}[0,T]$, $T>0$, denote the set of functions $f(t)$ for which $f \in C(-\infty,\infty)$ and f is T-periodic.*

Each function in $f \in C_{per}[0,T]$ can be identified with a function in $g \in C[0,T]$ for which $g(0) = g(T)$.

Using the formal solutions (5.6.1), (5.6.2), and the requirement that $m(0,t) = \mathcal{N}(t)$ and $\psi(0,t) = \mathcal{U}(t)$, we find that in order for periodic solutions to exist to problems $P(\lambda)$ and $P^*(\lambda)$, we must prove that there exist solutions to the following equations:

$$\mathcal{N}(t) = \int_0^\infty D_{in}(\tau,t)\exp\left(-\int_0^\tau \lambda I + D_{out}(\xi,\xi+t-\tau)\ d\xi\right)\mathcal{N}(t-\tau)\ d\tau =: L\mathcal{N}(t), \tag{5.6.3}$$

$$\mathcal{U}(t) = \int_0^\infty \exp\left(-\int_0^\tau \lambda I + D_{out}(\xi,\xi+t)\ d\xi\right) D_{in}^T(\tau,t+\tau)\mathcal{U}(t+\tau)\ d\tau =: L^*\mathcal{U}(t), \tag{5.6.4}$$

where $\mathcal{N},\mathcal{U} \in (C_{per}[0,T])^3$. To put this problem into a Banach space, the following norm is used:

$$||f(\cdot)|| = \max_{\substack{i\in\{1,2,3\}\\ t\in[0,T]}} |f_i(t)|, \tag{5.6.5}$$

for all $f \in (C_{per}[0,T])^3$. Note that from the choice of the norm in (5.6.5), the fact that the operators L and L^* are linear, and the fact that all components of the matrices D_{in} and $e^{D_{out}+\lambda I}$ are non-negative, we have an induced operator norm on L and L^* such that

$$||L|| = ||L\mathbb{I}||; \qquad ||L^*|| = ||L^*\mathbb{I}||,$$

where $\mathbb{I} = [1,1,1]^T$.

The integral operators on the right hand sides of (5.6.3) and (5.6.4) map any non-negative (non-zero) continuous periodic function to a strictly positive periodic function when $k_{G_1}(\tau,t)$, $k_S(\tau,t)$ and $k_{G_2}(\tau,t)$ are strictly positive. We then only need compactness of the operators in order to apply the Krein-Rutmann theorem.

We therefore make the following assumptions in order that the Krein-Rutmann theorem may be applied:

(K_1) The functions $k_p(\tau,t)$, $p \in \{G_1,S,G_2\}$ are strictly positive. (This assumption has been made in the statement of problem P but is restated here for convenience.)

(K_2) The minimum row sums of the matrices

$$\int_0^\infty D_{in}(\tau,t)e^{-\int_0^\tau D_{out}(\xi,\xi+t-\tau)\ d\xi}\ d\tau$$

and

$$\int_0^\infty e^{-\int_0^\tau D_{out}(\xi,t+\xi)\ d\xi} D_{in}^T(\tau,t+\tau)\ d\tau$$

are greater than or equal to one for $0 \le t \le T$.

Assumption (K_1) is needed for existence of solutions. Assumption (K_2) implies that the eigenvalue $\nu(0)$ is greater than one (this shall be proved below).

Theorem 5.6.4. *Assume that* $\lambda \geq 0$. *Then the operators* L *and* L^*, *defined by the equations* (5.6.3) *and* (5.6.4) *respectively, are compact.*

Proof. We shall prove the compactness of L and merely mention that the compactness of L^* is proved in a similar manner.

In order to prove the compactness of L it shall be shown that for any bounded subset $\mathcal{B}$ of functions of $[C_{per}[0,T]]^3$, the resulting transformed set $L\mathcal{B}$ is uniformly bounded and equicontinuous. In fact, if we define

$$\mathcal{B}_p = \{f \in C_{per}[0,T] : f = \mathcal{N}_p \ \text{ for some } \ \mathcal{N} \in \mathcal{B}\},$$
$$L\mathcal{B}_p = \{f \in C_{per}[0,T] : f = L\mathcal{N}_p \ \text{ for some } \ \mathcal{N} \in \mathcal{B}\},$$

and $L\mathcal{B}_p$ is uniformly bounded and equicontinuous for $p \in \{G_1, S, G_2\}$; then, by the Arzela-Ascoli theorem, it is found that for any sequence of functions $\mathcal{N}^m$, $m = 1, 2, \ldots$, in $\mathcal{B}$, the sequence $L\mathcal{N}^m$ has a convergent subsequence in $[C_{per}[0,T]]^3$. Thus, L is a compact operator. It therefore remains to be seen that $L\mathcal{B}_p$ is uniformly bounded and equicontinuous.

Uniform Boundedness: Let $B > 0$ be a constant such that $||\mathcal{N}|| \leq B$ for all $\mathcal{N} \in \mathcal{B}$. Then

$$\mathcal{N}_p(t) \leq B$$

for all $p \in \{G_1, S, G_2\}$ and $t \geq 0$. Further, let

$$A = \left|\left| \int_0^\infty D_{in}(\tau, t) e^{-\int_0^\tau \lambda I + D_{out}(\xi, \xi + t - \tau)\, d\xi} \mathbb{I} \, d\tau \right|\right|,$$

where, as above, $\mathbb{I} = [1, 1, 1]^T$. The constant A exists due to the assumptions made on $k_p(\tau, t)$ and $\mu_p(\tau, t)$, $p \in \{G_1, S, G_2\}$ in the statement of problem P. Note that $A = ||L||$.

Take any $\mathcal{N} \in \mathcal{B}$. Then, from (5.6.3), we find that

$$[L\mathcal{N}]_p(t) \leq AB$$

Since this applies for any $\mathcal{N} \in \mathcal{B}$, we see that LB_p is uniformly bounded.

Equicontinuity: Take any $\mathcal{N} \in \mathcal{B}$. Using (5.6.3), we find that

$$|L\mathcal{N}_p(t_0) - L\mathcal{N}_p(t)| \leq 2 \max_{p' \in \{G_1, S, G_2\}} \int_0^\infty B e^{-(\lambda + \mathcal{M})\tau} |k_{p'}(\tau, t_0) - k_{p'}(\tau, t)| \, d\tau,$$

where $\mathcal{M} > 0$ is a constant such that $k_p(\tau,t) + \mu_p(\tau,t) \geq \mathcal{M}$ for all $(\tau,t) \in [0,\infty) \times [0,\infty)$. (The factor of 2 comes from the fact that one of the components of $D_{in}(\tau,t)$ is $2k_{G_2}(\tau,t)$). The above integral exists since we have assumed when posing problem P that $k_p(\tau,t)$ is continuous and bounded for all $p \in \{G_1, S, G_2\}$ and $t \geq 0$. Now, due to the uniform continuity of k_p for all phases p, we find that for any $\varepsilon > 0$ there is some $\delta > 0$ such that when $|t_0 - t| < \delta$, we have

$$|L\mathcal{N}_p(t_0) - L\mathcal{N}_p(t)| \leq \varepsilon \int_0^\infty Be^{-(\lambda+\mathcal{M})\tau}\ d\tau = \frac{\varepsilon B}{\lambda + \mathcal{M}}.$$

Since $\mathcal{N}$ was arbitrary, we find that the set of functions LB_p is equicontinuous.

This completes the proof of the theorem. □

Now, using the notion of dual systems from [43] (see Appendix B), it can be shown that L and L^* are adjoint with respect to the dual system $\left\langle (C_{per}[0,T])^3, (C_{per}[0,T])^3 \right\rangle$, where the bilinear form $\langle \cdot, \cdot \rangle$ is defined by

$$\langle f, g \rangle = \int_0^T f^T(t) g(t)\ dt,$$

for all $f,\ g \in (C_{per}[0,T])^3$. Thus L and L^* have the same nonzero eigenvalues (with the same multiplicity) (See Theorem B.0.4 in Appendix B).

To apply the Krein-Rutmann Theorem, first let $K \subset [\mathcal{C}_{per}[0,T]]^3$ be the subset of periodic functions with non-negative components. It is easily checked that K is a closed proper convex cone. Now, we showed above in Theorem 5.6.4 that both operators L and L^*, defined by equations (5.6.3) and (5.6.4) are compact operators. We now claim the following result

Lemma 5.6.5. *For all $\mathcal{N}, \mathcal{U} \in K$, the functions $L\mathcal{N}$ and $L^*\mathcal{U}$ belong to K_I, the interior of the cone K (this is necessary in order to apply the second part of Theorem 5.6.2).*

Proof. Consider the operator L, defined by (5.6.3). By assumption (K_1) the coefficients $k_p(\tau,t)$ are strictly positive for all $p \in \{G_1, S, G_2\}$. Therefore, The integral expression in Equation (5.6.3) is strictly positive in all components when $\mathcal{N} \in K$ is not identically zero. Therefore $L\mathcal{N} \in K_I$.

Similarly we find that $L^*\mathcal{U} \in K_I$ when $0 \neq U \in K$. □

From the last two results, we may now apply the second part of the Krein-Rutmann theorem, so that we can state that there exists a principal, real eigenvalue ν for L and L^* depending on the parameter λ. We thus write $\nu = \nu(\lambda)$.

The aim now is to make the following argument, which shall be given as a proposition:

Proposition 5.6.6. *$\nu(0) > 1$ and $\nu(\lambda) \to 0$ as $\lambda \to \infty$. Moreover ν is continuously dependent on λ. Therefore, by the intermediate value theorem, there exists some $\lambda_0 > 0$ such that $\nu(\lambda_0) = 1$.*

The truth of Proposition 5.6.6 hinges on the continuous dependence of ν on λ. In [49], this argument is made for the case of a single-compartment age-distribution model. It was also suggested by Bell [11] in 1969 to find the steady-size distributions of the single-compartment model of cell-growth without dispersion. An example proof of the continuous dependence of an eigenvalue on a parameter, with full analytic detail, can be found in [70]. However in [70] the setting is a Hilbert space and the operator involved is self-adjoint. Here we are working in a Banach space (although it may be possible to work with the problem in L^2) with an operator that is not self-adjoint (in the sense of dual systems).

Continuous dependence of $\nu(\lambda)$ on λ is taken for granted in [49]. This may be acceptable in the case of compact, self-adjoint, linear operators in Hilbert spaces, where the principal eigenvalue is equal to the norm of the operator. In that case, if the norm were to vary continuosly with λ, the principal eigenvalue $\nu(\lambda)$ would also vary continuously. In the current setting, however, we need a more general result: one which applies for operators which are not self-adjoint. Such a result is found in [40] (Chapter 4, Theorem 3.16 and the following discussion). The result is more general than we need, but for compact operators on a real Banach space we may state as a corollary, the following theorem:

Theorem 5.6.7. *Let T and S be compact operators from a (real) Banach space X into itself. (This implies the spectra, $\sigma(T)$, $\sigma(S)$, are countable with no accumulation point different from zero, with each non-zero $\nu \in \sigma(T)$ or $\nu' \in \sigma(S)$ being an eigenvalue with finite multiplicity.)*

Suppose that T has a principal eigenvalue $\nu > 0$. Then for any $\varepsilon > 0$ there exists a $\delta > 0$ such that when

$$||S - T|| < \delta,$$

there is a principal eigenvalue $\nu' > 0$ of S satisfying $|\nu' - \nu| < \varepsilon$.

Thus, if the operators L and L^* vary continuously for $\lambda \geq 0$, we find that the principal eigenvalue $\nu(\lambda)$ must also vary continuously with λ. We shall now prove that this is indeed the case.

Theorem 5.6.8. *The operators L and L^* vary continuously with λ when $\lambda \geq 0$.*

Proof. We write L now as $L(\lambda)$ to signify its dependence on λ. First assume that $\lambda > 0$. We shall show that L varies continuously with λ. This is seen in the fact that

$$|[L(\lambda) - L(\lambda')]\mathcal{N}(t)| \leq \int_0^\infty D_{in}(\tau, t) \exp\left(-\int_0^\tau D_{out}(y, t + y - \tau)\, dy\right) |\mathcal{N}(t-\tau)||e^{-\lambda\tau} - e^{-\lambda'\tau}|\, d\tau,$$

where $|\mathcal{N}(t-\tau)|$ denotes the vector formed by taking absolute values of each component of $\mathcal{N}(t-\tau)$. Without loss of generality, assume that $||\mathcal{N}|| = 1$ (using the norm defined in (5.6.5)). We know that

$$D_{in}(\tau, t) \exp\left(-\int_0^\tau D_{out}(y, t+y-\tau)\ dy\right) |\mathcal{N}(t-\tau)|$$

is bounded in $[0,\infty) \times [0,\infty)$, since $D_{in}(\tau,t)$ is bounded and the components of $\mathcal{N}(t-\tau)$ and the exponential term never exceed one. Thus

$$|[L(\lambda) - L(\lambda')]\mathcal{N}(t)| \leq M \int_0^\infty |e^{-\lambda\tau} - e^{-\lambda'\tau}|\ d\tau,$$

for some constant M independent of $\mathcal{N}$. The right hand side of this expression tends to zero as $\lambda' \to \lambda$. Hence, $L(\lambda)$ varies continuously with λ when $\lambda > 0$.

Now assume that $\lambda = 0$. We find that, for $\lambda' > 0$,

$$\begin{aligned} |[L(0) - L(\lambda')]\mathcal{N}(t)| &\leq \int_0^\infty D_{in}(\tau,t) \exp\left(-\int_0^\tau D_{out}(y, t+y-\tau)\ dy\right) |\mathcal{N}(t-\tau)||1 - e^{-\lambda'\tau}|\ d\tau. \\ &\leq \int_0^\infty D_{in}(\tau,t) \exp\left(-\int_0^\tau D_{out}(y, t+y-\tau)\ dy\right) \mathbb{I}|1 - e^{-\lambda'\tau}|\ d\tau, \end{aligned}$$

where $\mathbb{I} = [1,1,1]^T$. But from the fact that $k_p(\tau,t) + \mu_p(\tau,t)$, $p \in \{G_1, S, G_2\}$ is bounded below by a constant, $\mathcal{M} > 0$, we know that

$$D_{in}(\tau, t) \exp\left(-\int_0^\tau D_{out}(y, t+y-\tau)\ dy\right) \mathbb{I}$$

has a finite integral on τ bounded for all $t \in [0,T]$. Thus, for any $\varepsilon > 0$ we may pick $\tau_0 > 0$ large enough such that

$$\int_{\tau_0}^\infty D_{in}(\tau,t) \exp\left(-\int_0^\tau D_{out}(y, t+y-\tau)\ dy\right) \mathbb{I}|1 - e^{-\lambda'\tau}|\ d\tau < \varepsilon,$$

and we may then pick $\lambda' > 0$ small enough such that

$$\int_0^{\tau_0} D_{in}(\tau,t) \exp\left(-\int_0^\tau D_{out}(y, t+y-\tau)\ dy\right) \mathbb{I}|1 - e^{-\lambda'\tau}|\ d\tau < \varepsilon.$$

So that for any $\varepsilon > 0$ there exists some $\delta > 0$ such that when $0 \leq \lambda' < \delta$, we have
$|[L(0) - L(\lambda')]\mathcal{N}(t)| \leq 2\varepsilon$. This implies the continuity of L with respect to λ for all $\lambda \geq 0$. The continuity of L^* is shown in a similar manner. $\square$

The other points on which Proposition 5.6.6 depends are that $\nu(0) > 1$ and $\nu(\lambda) \to 0$ as $\lambda \to \infty$. The fact that $\nu(\lambda) \to 0$ as $\lambda \to \infty$ is shown by considering first that

$$\nu(\lambda) \leq ||L(\lambda)|| = \left|\left|\int_0^\infty D_{in}(\tau,t) e^{-\int_0^\tau \lambda I + D_{out}(y,t+y-\tau)\ dy} \mathbb{I}\ d\tau\right|\right|,$$

where, again, $\mathbb{I} = [1, 1, 1]^T$. But as $\lambda \to \infty$, the right hand side of the above inequality tends to zero. Therefore $\nu(\lambda) \to 0$ as $\lambda \to \infty$.

We show that $\nu(0) > 1$ as follows:

Let $e_{\nu(0)}(t)$ denote the eigenfunction of L associated with the eigenvalue $\nu(0)$. Since, by the Krein-Rutmann theorem, $e_{\nu(0)}(t)$ is strictly positive, there exists a constant C such that

$$\min_{p \in \{G_1, S, G_2\}, 0 \le t \le T} C e_{\nu(0),p}(t) = 1.$$

Now, since the minima of $Ce_{\nu(0),p}(t)$ and $CLe_{\nu(0),p}(t)$ occur at the same points ($e_{\nu(0)}(t)$ is an eigenfunction), the eigenvalue $\nu(0)$ must be of the form

$$\nu(0) = \frac{\min_{p \in \{G_1, S, G_2\}, 0 \le t \le T} LCe_{\nu(0),p}(t)}{\min_{p \in \{G_1, S, G_2\}, 0 \le t \le T} Ce_{\nu(0),p}(t)} = \min_{p \in \{G_1, S, G_2\}, 0 \le t \le T} LCe_{\nu(0),p}(t)$$

Then, by the linearity of L, we find that

$$\nu(0) \ge \min_{p \in \{G_1, S, G_2\}, 0 \le t \le T} L\mathbb{I}_p.$$

But, by assumption (K_2), we find that

$$\min_{p \in \{G_1, S, G_2\}, 0 \le t \le T} L\mathbb{I}_p > 1,$$

and therefore it can be concluded that $\nu(0) > 1$.

This is the final point needed to show that Proposition 5.6.6 holds true. Therefore there exists some $\lambda_0 > 0$ such that $\nu(\lambda_0)$, the shared principal eigenvalue of L and L^*, is equal to one.

5.6.1 Stability of periodic solutions

Let $\lambda_0 > 0$ be the point at which the principal eigenvalue of L is equal to one. Then Equations (5.6.3) and (5.6.4) have solutions when $\lambda = \lambda_0$ and therefore periodic solutions $m(\tau, t)$ and $\psi(\tau, t)$ exist to problem $P(\lambda_0)$. It can also be checked that $m(\tau, t) \in (L^1 \cap L^\infty)([0, \infty) \times [0, T])$ and $\psi(\tau, t) \in L^\infty([0, \infty) \times [0, T])$ (due to the lower bound $\mathcal{M} > 0$ for $k_p(\tau, t) + \mu_p(\tau, t)$, $p \in \{G_1, S, G_2\}$) for any $T > 0$. Also, from Lemma 5.6.5, we know that $m(0, t)$ and $\psi(0, t)$ (the eigenfunctions of L and L^* respectively) are strictly positive.

We may thus apply Theorem 5.4.5 to any solution $n(\tau, t)$ of problem $P(\lambda_0)$ to show that

$$\int_0^\infty \psi^T(\tau, t) |n(\tau, t) - K^* m(\tau, t)| \, d\tau \to 0$$

as $t \to \infty$, where K^* is defined as in Theorem 5.4.5. Moreover, if $n(x, t)$ is a solution to problem P, then $n(\tau, t)e^{-\lambda_0 t}$ is a solution of problem $P(\lambda_0)$, so that we have the following general result:

Theorem 5.6.9. *Let $n(\tau,t)$ be a solution to problem P with initial conditions $n_0(\tau)$. Assume that (K_1) and (K_2) hold. Then there exists some $\lambda_0 > 0$ such that problem $P(\lambda_0)$ and $P^*(\lambda_0)$ have periodic solutions $m(\tau,t)$ and $\psi(\tau,t)$, with*

$$\int_0^\infty \psi^T(\tau,t)|n(\tau,t)e^{-\lambda_0 t} - K^* m(\tau,t)|\ d\tau \to 0$$

as $t \to \infty$, where

$$K^* = \int_0^\infty \psi(\tau,0) n_0(\tau)\ d\tau.$$

This means that if $n(\tau,t)$ describes the age-distribution of a population of cells, and solves problem P, then taking away any exponential growth or decay (by using a factor of $e^{-\lambda_0 t}$), the age-distribution of the cells exhibits periodic behaviour as $t \to \infty$ and is approximated by the periodic function $m(\tau,t)$.

Chapter 6

Analysis of a multi-compartment, age-size distribution model of cell-growth

We now study a multi-compartment age-size distribution model of cell growth which is related to the model first given in [3]. A modified version of the same model is studied in relation to modelling cell-death in populations exposed to the chemotheraputic agent paclitaxel in [5]. The model studied here has one less compartment than that of [3], which has compartments for G_1-, S-, G_2- and M-phases of cell-growth. Here the model only has compartments for G_1-, S- and G_2-phases of cell growth. This simplifies the mathematics somewhat but does not change the results drastically, since the G_2- and M-phase compartments behave similarly to each other in the model of [3].

The model here is structured by an age variable τ and size variable x. In this case, the 'age' of a cell is considered to be the time the cell has spent in its current growth-phase. Cells in this model age at a constant rate in all phases. They do not change in size unless they are in S-phase and they may only grow to a maximum size of $x = l$, for some $l > 0$. The maximum size l is introduced mainly so that we can use Sturm-Liouville theory when studying steady age-size distributions of the model (see the following sections).

Each phase has a specific death rate independent of age and size. The G_1 and G_2 phases have cell-transfer rates dependent on size and age, which specify the rate at which cells move out of their current phase and into the next phase of cell growth. Cells stay in S phase for a fixed period of time T_S, after which they immediately enter into G_2-phase.

The size variable, x, of this model represents DNA content of the cell. This is the reason why the size of a cell only changes in S-phase.

Note that the stability of the model is not studied in detail here. Results related to the stability of the model here are merely indicated. The existence of steady age-size distributions to the model is investigated in more detail.

6.1 The Model

The equations describing the evolution of the age-size distribution for G_1-, S- and G_2-phases are given below:

$$\frac{\partial}{\partial t}G_1(x,\tau,t) + \frac{\partial}{\partial \tau}G_1(x,\tau,t) = -(k_{G_1}(x,\tau) + \mu_{G_1})G_1(x,\tau,t) \tag{6.1.1}$$

$$\frac{\partial}{\partial t}S(x,\tau,t) + \frac{\partial}{\partial \tau}S(x,\tau,t) = D\frac{\partial^2 S}{\partial x^2}(x,\tau,t) - g\frac{\partial S}{\partial x}(x,\tau,t) - \mu_S S(x,\tau,t) \tag{6.1.2}$$

$$\frac{\partial}{\partial t}G_2(x,\tau,t) + \frac{\partial}{\partial \tau}G_2(x,\tau,t) = -(k_{G_2}(x,\tau) + \mu_{G_2})G_2(x,\tau,t), \tag{6.1.3}$$

where Equation (6.1.2) is valid in the region

$$0 \le x \le l; \qquad 0 \le \tau \le T_S; \qquad 0 < t < \infty,$$

and the others are valid in the region

$$0 \le x \le l; \qquad 0 < \tau, t < \infty.$$

We consider $S(x,\tau,t) = 0$ when $\tau > T_S$, since cells only spend a fixed time in S-phase.

As mentioned before, we impose the maximum cell size, $x = l$, in order to make the model easier to deal with mathematically (this also follows [4]). By convention we assume that the functions S, G_1 and G_2 are zero for $x > l$. As in the single-compartment model, the coefficient $g > 0$ represents the rate of increase in the size of a cell when in S-phase and is assumed to be positive. In this case g is the rate of synthesis of new DNA content in a cell. $D > 0$, the dispersion coefficient, represents stochastic variation in the growth process of each individual cell. The specific death rates in each phase, μ_{G_1}, μ_S and μ_{G_2} are assumed to be non-negative (they are permitted to be zero). The functions $k_{G_1}(x,\tau)$ and $k_{G_2}(x,\tau)$ represent the transfer rates of cells out of the phases G_1 and G_2 and into the S and G_1 respectively. They are assumed to be non-negative, bounded and uniformly continuous. Moreover we assume that there exists some $\mathcal{M} > 0$ such that

$$k_p(x,\tau) + \mu_p > \mathcal{M}$$

for all $p \in \{G_1, G_2\}$ and $(x, \tau) \in [0, l] \times [0, \infty)$. In fact, define

$$0 < \mathcal{M} = \inf k_p(x, \tau) + \mu_p, \tag{6.1.4}$$

over all $p \in \{G_1, G_2\}$ and $(x, \tau) \in [0, l] \times [0, \infty)$. Finally, we assume that for any fixed $x \geq 0$, the function $k_p(x, \tau)$, $p \in \{G_1, G_2\}$ is not identically zero on $0 \leq \tau < \infty$. These assumptions are mainly technical.

The fact that cells spend a fixed time in S-phase (following [3], [4] and [5]) means that cells with any DNA content can divide. This is not a feature of healthy cells, which have a specific DNA content at which they divide. This model, however, is not intended to model healthy cells, but is intended for tumour cells growing in vitro. These cells are more susceptible to variation in DNA content [44]. Also, in practice, the dispersion coefficient D is kept small, so that the majority of cells will be in a tight range about a fixed division-size when they divide.

When new cells are produced by cell-division, they are introduced into their new phase at age $\tau = 0$, so that all of the inputs to each individual phase are taken care of by boundary conditions at $\tau = 0$. The boundary conditions for the model are given below. Those that are due to the transfer of cells from one phase to another are (6.1.5),(6.1.6) and (6.1.8):

$$G_1(x, 0, t) = 4 \int_0^\infty k_{G_2}(2x, \tau) G_2(2x, \tau, t) \, d\tau, \tag{6.1.5}$$

$$S(x, 0, t) = \int_0^\infty k_{G_1}(x, \tau) G_1(x, \tau, t) \, d\tau, \tag{6.1.6}$$

$$DS_x(0, \tau, t) - gS(0, \tau, t) = DS_x(l, \tau, t) - gS(l, \tau, t) = 0, \tag{6.1.7}$$

$$G_2(x, 0, t) = S(x, T_S, t), \tag{6.1.8}$$

where the ranges of x, τ and t for the above boundary conditions are given as:

$$0 \leq x \leq l; \qquad 0 \leq \tau < \infty; \qquad 0 < t < \infty.$$

Since we consider $G_2(x, \tau, t) = 0$ when $x > l$, the boundary condition (6.1.5) specifies $G_1(x, 0, t) = 0$ when $x > l/2$. Note also, that the boundary condition (6.1.5) takes into account that when cells leave G_2-phase, they divide into two daughter cells which start their cell-cycle in G_1-phase. The number of cells introduced at age $\tau = 0$ in G_1-phase between times $t_0 < t_1$ is thus

$$\int_{t_0}^{t_1} \int_0^l G_1(x, 0, t) \, dx \, dt = 2 \int_{t_0}^{t_1} \int_0^l \int_0^\infty k_{G_2}(x, \tau) G_2(x, \tau, t) \, d\tau \, dx \, dt;$$

twice the number of cells which divide in the same period of time.

The boundary conditions (6.1.7) are zero flux boundary conditions at sizes $x = 0$ and $x = l$ in S-phase. This ensures that no cells pass through size $x = 0$ or $x = l$; that is, no cells leave the region $0 \leq x \leq l$ and no cells enter from outside the same region. The boundary condition (6.1.8) expresses that when cells have spent time T_S in S-phase, they immediately transfer into G_2-phase. For this reason, we consider $S(x, \tau, t) = 0$ when $\tau > T_S$.

Finally, we wish for solutions where every component is in non-negative in $L^1([0, l] \times [0, \infty) \times [0, T])$ for any $T > 0$ and for which every component tends to zero as $\tau \to \infty$.

We assume that the initial conditions of the model $G_1(x, \tau, 0)$, $S(x, \tau, 0)$ and $G_2(x, \tau, 0)$ are all non-negative and in $L^1([0, l] \times [0, \infty))$. Additional assumptions may be needed to prove stability of the model, but in the following sections we are more interested in proving the existence of steady age-size distributions.

6.2 Steady Age-Size Distributions of the model

Since we are dealing with a population of cells structured by both age and size, we are interested here in age-size distributions which are preserved by the model described above. Steady Age-Size Distributions SASDs of the model (6.1.1)-(6.1.8), should any exist, are (non-negative) solutions of the problem:

$$\frac{\partial}{\partial \tau} G_1(x, \tau) = -(k_{G_1}(x, \tau) + \mu_{G_1} + \lambda) G_1(x, \tau), \tag{6.2.1}$$

$$\frac{\partial}{\partial \tau} S(x, \tau) = D \frac{\partial^2 S}{\partial x^2}(x, \tau) - g \frac{\partial S}{\partial x}(x, \tau) - (\mu_S + \lambda) S(x, \tau) \tag{6.2.2}$$

$$\frac{\partial}{\partial \tau} G_2(x, \tau) = -(k_{G_2}(x, \tau) + \mu_{G_2} + \lambda) G_2(x, \tau), \tag{6.2.3}$$

where Equation (6.2.2) is valid in the region

$$0 \leq x \leq l, 0 < \tau \leq T_S,$$

while the other equations are valid for $0 \leq x \leq l$, $0 < \tau < \infty$. The SASDs also satisfy the boundary conditions (6.1.5)-(6.1.8) (without any dependence on t). The equations above come from assuming a solution of the form

$$G_1(x, \tau, t) = e^{\lambda t} G_1(x, \tau); \qquad S(x, \tau, t) = e^{\lambda t} S(x, \tau); \qquad G_2(x, \tau, t) = e^{\lambda t} G_2(x, \tau).$$

As was specified for the general model in the previous section, we require that each component of the SASD should be in $L^1([0, l] \times [0, \infty))$, with $S(x, \tau)$ only having support for $0 \leq \tau \leq T_S$.

We can easily solve for G_1 and G_2 in terms of $G_1(x, 0)$ and $G_2(x, 0)$, giving the following:

$$G_1(x, \tau) = G_1(x, 0) \exp\left(-\int_0^\tau k_{G_1}(x, s) + \mu_{G_1} + \lambda \, ds\right), \tag{6.2.4}$$

$$G_2(x, \tau) = G_2(x, 0) \exp\left(-\int_0^\tau k_{G_2}(x, s) + \mu_{G_2} + \lambda \, ds\right). \tag{6.2.5}$$

These solutions are in $L^1([0,l]\times[0,\infty))$ when $G_1(x,0)$ and $G_2(x,0)$ are bounded for $0\le x\le l$ and $\lambda > -\mathcal{M}$, where $\mathcal{M}$ is defined by Equation (6.1.4). (This is because when $\lambda > -\mathcal{M}$, the exponential functions above are less than or equal to $e^{-(\mathcal{M}+\lambda)\tau}$, so we find that $G_1(x,\tau)$, $G_2(x,\tau) = O(e^{-\varepsilon\tau})$ for some $\varepsilon > 0$.)

Substituting

$$S(x,\tau) = m(x,\tau)\exp\left[\frac{gx}{2D} - \tau\left(\frac{g^2}{4D} + \mu_S + \lambda\right)\right],$$

transforms the SASD equation for S into the heat equation on a bounded domain:

$$\begin{cases} m_\tau(x,\tau) = Dm_{xx}(x,\tau), & 0\le x\le l,\ 0<\tau\le T_S, \\ Dm_x(x,\tau) - \frac{g}{2}m(x,\tau)|_{x=0,l} = 0, & \tau > 0. \end{cases} \tag{6.2.6}$$

The eigenvalues, η_n for the associated Sturm-Liouville problem are

$$\eta_n = \frac{n^2\pi^2}{l^2}, \qquad n = 1,2,3,\dots, \tag{6.2.7}$$

with the associated eigenfunctions ϕ_n being

$$\phi_n(x) = \cos\frac{n\pi x}{l} + \frac{gl}{2\pi n D}\sin\frac{n\pi x}{l}, \tag{6.2.8}$$

and

$$\eta_0 = -\frac{g^2}{4D^2}. \tag{6.2.9}$$

with associated eigenfunction

$$\phi_0(x) = e^{\frac{gx}{2D}}. \tag{6.2.10}$$

This gives us the following formal solution for $m(x,\tau)$ in terms of the eigenfunctions:

$$m(x,\tau) = \sum_{n=0}^{\infty} e^{-\eta_n D\tau}\frac{\phi_n(x)}{||\phi_n||^2}\int_0^l \phi_n(\xi)e^{-\frac{g\xi}{2D}}S(\xi,0)\ d\xi, \tag{6.2.11}$$

where $||\phi_n||$ is the L^2-norm of ϕ_n on the region $[0,l]$. However, using the boundary conditions (6.1.5), (6.1.6) and (6.1.8), as well as the solutions (6.2.4), (6.2.5), we may express $S(x,0)$ in terms of $S(x,T_S)$ as follows:

$$\begin{aligned} S(x,0) = &\int_0^\infty k_{G_1}(x,\tau)\exp\left(-\int_0^\tau k_{G_1}(x,s)+\mu_{G_1}+\lambda\ ds\right)d\tau \\ &\times 4\int_0^\infty k_{G_2}(2x,\tau)\exp\left(-\int_0^\tau k_{G_2}(2x,s)+\mu_{G_2}+\lambda\ ds\right)d\tau\times S(2x,T_S). \\ = &\ \Gamma(x;\lambda)S(2x,T_S), \end{aligned} \tag{6.2.12}$$

where we have used $\Gamma(x;\lambda)$ to denote the product of the above integrals (6.2.12). Note that because we have assumed, for any fixed $x\ge 0$ that $k_p(x,\tau)$ is not identically zero on $0\le\tau<\infty$, we find that $\Gamma(x;\lambda) > 0$ for any $0\le x\le l$.

By convention we assume that $S(x,\tau) = 0$ when $x > l$, so that Equation (6.2.12) implies $S(x,0) = 0$ for $x > l/2$. Multiplying (6.2.11) by

$$\exp\left[\frac{gx}{2D} - \tau\left(\frac{g^2}{4D} + \mu_S + \lambda\right)\right],$$

we derive an expression for $S(x,\tau)$. Substituting the expression obtained for $S(2x,T_S)$ from this into (6.2.12) then gives the following Fredholm integral equation for $S(x,0)$ for $0 \leq x \leq l/2$:

$$\begin{aligned} S(x,0) &= e^{\frac{gx}{D} - T_S\left(\frac{g^2}{4D} + \mu_S + \lambda\right)} \Gamma(x;\lambda) \int_0^{l/2} \sum_{n=0}^{\infty} e^{-\eta_n D T_S} \frac{\phi_n(2x)}{||\phi_n||^2} \phi_n(\xi) e^{\frac{-g\xi}{2D}} S(\xi,0)\, d\xi \\ &=: LS(x,0). \end{aligned} \tag{6.2.13}$$

We aim to find a suitable λ such that the above integral equation for $S(x,0)$ on $0 \leq x \leq l/2$ has a solution. If we can solve this equation (we aim to find a solution in $C[0,l/2]$), then from the solution $S(x,0)$ we can produce a SASD by evolving $S(x,\tau)$ according to (6.2.11) and then using equations (6.2.4), (6.2.5) along with the boundary conditions (6.1.5), (6.1.6) and (6.1.8). Thus if we can solve (6.2.13), then a solution to equations (6.2.1)-(6.2.3) exists, satisfying the boundary conditions (6.1.5)-(6.1.8) (without any dependence on t).

The problem of finding a λ such that Equation (6.2.13) has a solution is addressed in Section 6.4 and 6.5.

6.3 Dual SASDs of the model

The dual SASD problem for the model can be written as follows:

$$\frac{\partial}{\partial \tau} G_1^*(x,\tau) = (k_{G_1}(x,\tau) + \mu_{G_1} + \lambda) G_1^*(x,\tau) - k_{G_1}(x,\tau) S^*(x,0), \tag{6.3.1}$$

$$\frac{\partial}{\partial \tau} S^*(x,\tau) = -D \frac{\partial^2 S^*}{\partial x^2}(x,\tau) - g \frac{\partial S^*}{\partial x}(x,\tau) + (\mu_S + \lambda) S^*(x,\tau), \tag{6.3.2}$$

$$\frac{\partial}{\partial \tau} G_2^*(x,\tau) = (k_{G_2}(x,\tau) + \mu_{G_2} + \lambda) G_2^*(x,\tau) - 2k_{G_2}(x,\tau) G_1^*(x/2,0), \tag{6.3.3}$$

Again, equation (6.3.2) is valid in the region

$$0 \leq x \leq l, \qquad 0 < \tau \leq T_S,$$

while the others are valid for $0 \leq x \leq l$, $0 < \tau < \infty$. The boundary conditions are as follows:

$$S^*(x,T_S) = G_2^*(x,0); \qquad S_x^*(0,\tau) = S_x^*(l,\tau) = 0, \tag{6.3.4}$$

for $0 \leq x \leq l$ and $0 \leq \tau < \infty$. We specify that the G_1^* and G_2^* compartments of the dual SASD should be non-negative and in $L^\infty([0,l] \times [0,\infty))$, while the S^* compartment should be non-negative in the region $[0, l] \times [0, T_S]$ and in $L^\infty([0, l] \times [0, T_S])$, and we consider $S^*(x, \tau)$ to be zero when $\tau > T_S$.

The dual SASD problem is obtained similarly to Chapter 3 and 5. Let

$$N(x, \tau) = [G_1(x, \tau), S(x, \tau), G_2(x, \tau)]^T; \qquad \Psi(x, \tau) = [G_1^*(x, \tau), S^*(x, \tau), G_2^*(x, \tau)]^T,$$

and let $\mathcal{A}$ be the differential operator on N defined by equations (6.1.1)-(6.1.3), such that those equations may be expressed as

$$\mathcal{A}N = 0.$$

The dual SASD equations arise from the equation $\mathcal{A}^*\Psi = 0$, where $\mathcal{A}^*$ is constructed such that

$$\int_0^l \int_0^\infty \Psi^T(x, \tau)\mathcal{A}N(x, \tau)\ d\tau dx = \int_0^l \int_0^\infty N^T(x, \tau)\mathcal{A}^*\Psi(x, \tau)\ d\tau dx.$$

We obtain $\mathcal{A}^*$ via integration by parts, with the boundary conditions on S^* being imposed so that terms which arise outside the integral sign (in the process of integration by parts) are reduced to zero. For the above integrals to exist, a sufficient condition is that each component of N and $\mathcal{A}N$ belong to $L^1([0, l] \times [0, \infty))$ and that each component of Ψ and $\mathcal{A}^*\Psi$ belong to $L^\infty([0, l] \times [0, \infty))$.

Using the notion of dual systems ([43], Appendix B) we may say that $\mathcal{A}$ and $\mathcal{A}^*$ are adjoint with respect to the dual systems $\langle X_1, Y_1\rangle$ and $\langle X_2, Y_2\rangle$, where the bilinear form $\langle\cdot, \cdot\rangle$ is defined by

$$\langle f, g\rangle = \int_0^l \int_0^\infty f^T(x, \tau)g(x, \tau)\ dx\ d\tau,$$

and the spaces X_1, X_2, Y_1 and Y_2 are specified below, (in order that $\mathcal{A}^*$ may be obtained from $\mathcal{A}$ by integration by parts):

- X_1 is the set of vector valued functions $N(x, \tau)$ such that:
  - G_1, G_2, $G_{1,\tau}$, $G_{2,\tau}$ are continuous with respect to τ for any given $0 \le x \le l$, $0 \le \tau < \infty$ and $G_1(x, \tau)$, $G_2(x, \tau) \to 0$ as $\tau \to \infty$.
  - S has support contained in $[0, l] \times [0, T_S]$. S is continuous with respect to x and τ at any given point $0 \le x \le l$ and $0 \le \tau \le T_S$. S_x and S_{xx} are continuous with respect to x for any $0 \le x \le l$, $0 < \tau < T_S$, and S_τ is continuous with respect to τ for any $0 \le x \le l$, $0 < \tau < T_S$.
  - N satisfies the boundary conditions (6.1.5)-(6.1.8), (without any dependence on t). The components of N and their derivatives under the action of $\mathcal{A}$ are in $L^1([0, l] \times [0, \infty))$.
- X_2 is the set of vector valued functions $\{\mathcal{A}N : N \in X_1\}$.

- Y_1 is the set of vector valued functions $\{\mathcal{A}^*\Psi : \Psi \in Y_2\}$.

- Y_2 is the set of vector valued functions $\Psi(x,\tau)$ such that:

  - G_1^*, G_2^*, $G_{1,\tau}^*$, $G_{2,\tau}^*$ are continuous with respect to τ for any given $0 \le x \le l$, $0 \le \tau < \infty$.
  - S^* has support contained in $[0,l] \times [0,T_S]$. S^* is continuous with respect to x and τ at any given point, $0 \le x \le l$ and $0 \le \tau \le T_S$. S_x^* and S_{xx}^* are continuous with respect to x for any $0 \le x \le l$, $0 < \tau < T_S$, and S_τ^* is continuous with respect to τ for any $0 \le x \le l$, $0 < \tau < T_S$.
  - Ψ satisfies the boundary conditions in (6.3.4). The components of Ψ and their derivatives under the action of $\mathcal{A}^*$ are in $L^\infty([0,l] \times [0,\infty))$.

with X_1, X_2, Y_1 and Y_2 being supplied with any suitable norms. $\mathcal{A}$ maps X_1 to X_2 while $\mathcal{A}^*$ maps Y_2 to Y_1. Thus

$$\langle \mathcal{A}N, \Psi \rangle = \langle N, \mathcal{A}^*\Psi \rangle ,$$

for $N \in X_1$, $\Psi \in Y_2$.

Assuming a suitably smooth and integrable solution to the problem (6.1.1)-(6.1.8), we should be able to derive nice properties of the dual SASD in a similar way to Chapters 3 and 5. That is, similarly to Theorems 3.2.1 and 3.2.2 in Chapter 3, and Lemma 5.3.3 in Chapter 5, we ought to have the following result:

Theorem 6.3.1. *Let $n(x,\tau,t)$ be a solution to problem* (6.1.1)-(6.1.8) *with initial conditions $n(x,\tau,0) = n_0(x,\tau)$. Let $N(x,\tau)$ and $\Psi(x,\tau)$ be a SASD and dual SASD corresponding to some λ. Then*

$$\int_0^l \int_0^\infty \Psi^T(x,\tau) n(x,\tau,t) e^{-\lambda t} \, d\tau dx = \int_0^l \int_0^\infty \Psi(x,\tau) n_0(x,\tau) e^{-\lambda t} \, d\tau dx \tag{6.3.5}$$

for all $t \ge 0$, and the quantity

$$\int_0^l \int_0^\infty \Psi^T(x,\tau) |n(x,\tau,t)e^{-\lambda t} - KN(x,\tau)| \, d\tau dx \tag{6.3.6}$$

is non-increasing when $t > 0$ for any constant K.

This theorem is stated without proof. It is merely mentioned that the proofs of equations (6.3.5) and (6.3.6) will be similar to the proofs of Theorems 3.2.1 and 3.2.2 from Chapter 3 respectively.

Presently we shall examine the existence of a solution to the dual SASD problem. The dual SASD problem is easily solved for G_1^* and G_2^* by using an integrating factor in either case, giving

$$G_1^*(x,\tau) = \exp\left(\int_0^\tau k_{G_1}(x,s) + \mu_{G_1} + \lambda \; ds\right) \times \left(G_1^*(x,0) - S^*(x,0)\int_0^\tau k_{G_1}(x,s)\exp\left[-\int_0^s k_{G_1}(x,\rho) + \mu_{G_1} + \lambda \; d\rho\right] \; ds\right) \tag{6.3.7}$$

$$G_2^*(x,\tau) = \exp\left(\int_0^\tau k_{G_2}(x,s) + \mu_{G_2} + \lambda \; ds\right) \times \left(G_2^*(x,0) - 2G_1^*(x/2,0)\int_0^\tau k_{G_2}(x,s)\exp\left[-\int_0^s k_{G_2}(x,\rho) + \mu_{G_2} + \lambda \; d\rho\right] \; ds\right). \tag{6.3.8}$$

In order that G_1^* and G_2^* remain bounded, we impose the following conditions on $G_1^*(x,0)$ and $G_2^*(x,0)$:

$$G_1^*(x,0) = S^*(x,0)\int_0^\infty k_{G_1}(x,\tau)\exp\left(-\int_0^\tau k_{G_1}(x,s) + \mu_{G_1} + \lambda \; ds\right) \; d\tau \tag{6.3.9}$$

$$G_2^*(x,0) = 2G_1^*(x/2,0)\int_0^\infty k_{G_2}(x,\tau)\exp\left(-\int_0^\tau k_{G_2}(x,s) + \mu_{G_2} + \lambda \; ds\right) \; d\tau. \tag{6.3.10}$$

The solutions $G_1^*(x,\tau)$ and $G_2^*(x,\tau)$ above are valid when $\lambda > -\mathcal{M}$, where $\mathcal{M}$ is defined in Equation (6.1.4)

Now, substituting

$$S^*(x,\tau) = m^*(x,\tau)\exp\left[-\frac{g}{2D}x + \tau\left(\frac{g^2}{4D} + \mu_S + \lambda\right)\right],$$

transforms the SASD equation for S^* into the inhomogeneous (reverse) heat equation problem:

$$\begin{cases} m_\tau^*(x,\tau) = -Dm_{xx}^* & 0 \le x \le l, \; \tau > 0, \\ Dm_x^*(x,\tau) - \frac{g}{2}m^*(x,\tau)|_{x=0,l} = 0, & \tau > 0. \end{cases}$$

The associated Sturm-Liouville problem is the same as before.

The boundary condition, $S^*(x,T_S) = G_2^*(x,0)$ gives the following equation for $S^*(x,\tau)$:

$$S^*(x,\tau) = e^{-\frac{gx}{2D} + (\tau - T_S)\left(\frac{g^2}{4D} + \mu_S + \lambda\right)}\sum_{n=0}^\infty e^{\eta_n D(\tau - T_S)}\frac{\phi_n(x)}{||\phi_n||^2}\int_0^L \phi_n(\xi)e^{\frac{g\xi}{2D}}G_2^*(\xi,0) \; d\xi,$$

for $0 \le x \le l$, $0 \le \tau \le T_S$, where the eigenvalues η_n and eigenfunctions ϕ_n are specified in Equations (6.2.7)-(6.2.10). Using the boundary conditions (6.3.9), (6.3.10), we then find a Fredholm integral equation for $S^*(x,0)$ on $0 \le x \le l/2$:

$$\begin{aligned} S^*(x,0) &= e^{-\frac{gx}{2D} - T_S\left(\frac{g^2}{4D} + \mu_S + \lambda\right)}\int_0^l \sum_{n=0}^\infty \frac{1}{2}\Gamma\left(\frac{\xi}{2};\lambda\right)e^{-\eta_n D T_S}\frac{\phi_n(x)}{||\phi_n||^2}\phi_n(\xi)e^{\frac{g\xi}{2D}}S^*(\xi/2,0) \; d\xi. \\ &=: L^*S^*(x,0). \end{aligned} \tag{6.3.11}$$

If we can solve this equation for $0 \le x \le l/2$, then $S^*(x,0)$ on $0 \le x \le l$ using (6.3.11) again. Then using the boundary conditions (6.3.9), (6.3.10) and the explicit solutions for $G_1^*(x,\tau)$ and $G_2^*(x,\tau)$ in equations (6.3.7) and (6.3.8), we can produce a full dual SASD solution to our model.

6.4 Theory related to the question of the existence of a SASD/dual SASD pair

The operators L and L^*, obtained in the previous two sections, are adjoint with respect to the dual system (see Appendix B) $\langle C[0,l/2], C[0,l/2]\rangle$, where the space $C[0,l/2]$ is supplied with the supremum norm and the bilinear form $\langle \cdot,\cdot\rangle$ is defined by

$$\langle f,g\rangle = \int_0^{l/2} f(x)g(x)\ dx.$$

If we can prove that the operators are compact in $C[0,l/2]$, then since they are adjoint, they have the same (non-zero) eigenvalues with the same multiplicity (see Theorem B.0.4 in Appendix B).

If we can then prove that L and L^* are positive operators on $C[0,l/2]$, then we can use the Krein-Rutman Theorem (see Theorem 5.6.2, Section 5.6, Chapter 5) on the cone K of non-negative functions in $C[0,l/2]$ to show that L and L^* share a principal eigenvalue with corresponding positive eigenfunctions.

Let us assume for the moment that the positivity and compactness of L and L^* has been proved and let $\nu(\lambda)$ be the common principal eigenvalue (dependent on the value of λ) of the two operators. By Theorem 5.6.7, if L varies continuously with λ (that is, if $||L(\lambda) - L(\lambda+h)|| \to 0$ as $h \to 0$ for a given value of λ), then $\nu(\lambda)$ must also vary continuously with λ. We then wish to find two values λ_1 and λ_2 such that $\nu(\lambda_1) < 1$ and $\nu(\lambda_2) > 1$. If two such values can be found we then know, by the Intermediate Value Theorem, that there exists some λ_0 between λ_1 and λ_2 such that $\nu(\lambda_0) = 1$.

From the eigenfunctions, $S(x,0)$ and $S^*(x,0)$, of L when $\nu(\lambda_0) = 1$, we can then find a full steady age-size distribution $N(x,\tau)$ and dual steady age-size distribution $\Psi(x,\tau)$ using the appropriate boundary conditions and explicit solutions in Section 6.2 and 6.3.

When we specified the cell-growth model at the beginning of this chapter, we assumed that $k_p(x,\tau) + \mu_p$ was bounded below by some number $\mathcal{M} > 0$, for $p \in \{G_1, G_2\}$ and $(x,\tau) \in [0,l] \times [0,\infty)$ (recall the definition of $\mathcal{M}$ from Equation (6.1.4)). We often assume below that $\lambda > -\mathcal{M}$. This guarantees that the exponential terms in $\Gamma(x;\lambda)$ are $O(e^{-\varepsilon\tau})$ for some $\varepsilon > 0$, and also that $\Gamma(x;\lambda)$ varies continuously with λ and x. This is mentioned below in more detail when the need arises. This assumption also helps to guarantee that the expressions for $G_1(x,\tau)$ and $G_2(x,\tau)$ in (6.2.1) and (6.2.3) are in $L^1([0,l]\times[0,\infty))$; and that $G_1^*(x,\tau)$ and $G_2^*(x,\tau)$ in (6.3.7) and (6.3.8) are in $L^\infty([0,l]\times[0,\infty))$.

Theorem 6.4.1. *Assume that $-\mathcal{M} < \lambda \in \mathbb{R}$. Then the operators L and L^* are compact in $C[0,l/2]$.*

Proof. The aim of this proof is to show that any bounded set of functions in $C[0, l/2]$ is mapped by L into a uniformly bounded, equicontinuous set of functions. Thus we find that L is a compact operator by the Arzela-Ascoli theorem (See Appendix A). The proof for L^* is similar.

Let $\mathcal{B}$ be a bounded set of functions in $C[0, l/2]$. And let M be a constant such that $M \geq ||f||_{L^2[0,l/2]}$ for all $f \in \mathcal{B}$.

Using the Cauchy-Schwarz Inequality on Equation (6.2.13), we find that

$$|Lf(x)| \leq e^{\frac{gx}{D} - T_S\left(\frac{g^2}{4D} + \mu_S + \lambda\right)} \Gamma(x;\lambda) \sum_{n=0}^{\infty} e^{-\eta_n D T_S} \frac{|\phi_n(2x)|}{||\phi_n||} ||e^{\frac{-g\cdot}{2D}} f(\cdot)||_{L^2[0,l/2]}$$

Let

$$\sigma(x) = \sum_{n=0}^{\infty} e^{-\eta_n D T_S} \frac{|\phi_n(2x)|}{||\phi_n||}.$$

The right-hand side of the above equation is a uniformly convergent series of continuous functions. Therefore $\sigma(x)$ is continuous. Thus

$$\begin{aligned} |Lf(x)| &\leq e^{\frac{gx}{D} - T_S\left(\frac{g^2}{4D} + \mu_S + \lambda\right)} \Gamma(x;\lambda)\sigma(x)||f||_{L^2[0,l/2]} \\ &\leq \sup_{x \in [0,l/2]} M e^{\frac{gx}{D}} \Gamma(x;\lambda)\sigma(x), \end{aligned}$$

for all $f \in \mathcal{B}$. Therefore the set of functions $L\mathcal{B}$ is uniformly bounded.

To show that the set of functions $L\mathcal{B}$ is equicontinuous, we examine $|Lf(x) - Lf(y)|$ for any $f \in \mathcal{B}$. Similar to the working above, we find that $|Lf(x) - Lf(y)|$ is less than or equal to

$$Me^{-T_S\left(\frac{g^2}{4D} + \mu_S + \lambda\right)} \sum_{n=0}^{\infty} \frac{1}{||\phi_n||} e^{-\eta_n D T_S} \left| e^{\frac{gx}{D}} \Gamma(x;\lambda)\phi_n(2x) - e^{\frac{gy}{D}} \Gamma(y;\lambda)\phi_n(2y) \right|. \qquad (6.4.1)$$

By the fact that k_{G_1} and k_{G_2} are uniformly continuous, and using the assumption that $\lambda > -\mathcal{M}$, we find that $\Gamma(x;\lambda)$ is continuous on $[0, l/2]$. Thus, the functions

$$e^{\frac{gx}{D}} \Gamma(x;\lambda)\phi_n(2x),$$

which are continuous on the compact interval $[0, l/2]$, are uniformly continuous on the same interval $[0, l/2]$. Moreover, the infinite sum in (6.4.1) converges uniformly for all $x, y \in [0, l/2]$. Therefore, for any $\varepsilon > 0$ we may choose some $N > 0$ and $\delta > 0$ such that for $x, y \in [0, l/2]$, $|x - y| < \delta$, we have

$$Me^{-T_S\left(\frac{g^2}{4D} + \mu_S + \lambda\right)} \sum_{n=0}^{N} \frac{1}{||\phi_n||} e^{-\eta_n D T_S} \left| e^{\frac{gx}{D}} \Gamma(x;\lambda)\phi_n(2x) - e^{\frac{gy}{D}} \Gamma(y;\lambda)\phi_n(2y) \right| < \varepsilon/2,$$

due to the uniform continuity of the functions $e^{\frac{gx}{D}} \Gamma(x;\lambda)\phi_n(2x)$, and

$$Me^{-T_S\left(\frac{g^2}{4D} + \mu_S + \lambda\right)} \sum_{n=N+1}^{\infty} \frac{1}{||\phi_n||} e^{-\eta_n D T_S} \left| e^{\frac{gx}{D}} \Gamma(x;\lambda)\phi_n(2x) - e^{\frac{gy}{D}} \Gamma(y;\lambda)\phi_n(2y) \right| < \varepsilon/2,$$

due to the uniform convergence of the infinite sum. Thus, for any $\varepsilon > 0$ we may choose a $\delta > 0$ such that $|Lf(x) - Lf(y)| < \varepsilon$ when $x, y \in [0, l/2]$, $|x - y| < \delta$ for all $f \in \mathcal{B}$. This shows that the set of functions $L\mathcal{B}$ is equicontinuous.

Thus, for any sequence of functions f_m, $m = 1, 2, \dots$ in $\mathcal{B}$, the sequence of functions Lf_m contains a uniformly convergent subsequence. Therefore L maps any bounded sequence in $C[0, l/2]$ to a sequence containing a convergent subsequence in $C[0, l/2]$. This shows that L is a compact operator.

As mentioned at the beginning of this proof, we can show that L^* is a compact operator in a similar way. $\square$

The cone K: In order to apply the Krein-Rutman theorem we need to have a closed proper convex cone K on which L and L^* act. Take K to be the set of non-negative functions in $C[0, l/2]$. It is easy to check that K satisfies the properties of a proper convex cone from Definition 5.6.1 and that K is closed under the supremum norm. In order to apply the Krein-Rutman Theorem, we must first prove the following result:.

Theorem 6.4.2. *Let $\lambda > -\mathcal{M}$ and let K be the closed proper convex cone described above. Then L and L^* map K into itself. Moreover, when f is not identically zero, $Lf(x)$, $L^*f(x) > 0$ when $0 < x < l/2$.*

We now state two results needed in order to prove Theorem 6.4.2; they shall be proved at the end of this chapter in Section 6.8.

Theorem 6.4.3. *If $f(x)$ is continuous and $f'(x)$, $f''(x)$ are piecewise continuous on $[0, l]$ (with finitely many jumps), and if*

$$Df'(0) - \frac{g}{2}f(0) = Df'(l) - \frac{g}{2}f(l) = 0,$$

then the expression

$$m(x, \tau) = \int_0^l \sum_{n=0}^{\infty} e^{-\eta_n D\tau} \frac{\phi_n(x)}{||\phi_n||^2} \phi_n(\xi) f(\xi)\, d\xi$$

is continuous for all $0 \leq x \leq l$ and $0 \leq \tau \leq T_S$.

Theorem 6.4.4. *The set of functions $0 < f(x)$, which are continuous in $[0, l]$ and piecewise C^∞ in $[0, l]$ (with finitely many points of discontinuity in the derivatives) and satisfy the boundary conditions*

$$Df'(0) - \frac{g}{2}f(0) = Df'(l) - \frac{g}{2}f(l) = 0,$$

are dense in the subset of non-negative functions in $L^2[0, l]$.

We now prove Theorem 6.4.2 with the help of the above results:

Proof of Theorem 6.4.2. Consider the expression for Lf as given in Equation (6.2.13). In the proof of Theorem 6.4.1, we saw that when $\lambda > -\mathcal{M}$, L maps any bounded set of functions in $C[0, l/2]$ to an *equicontinuous* set of functions. The definition of equicontinuity (see Appendix A) implies that each f in the transformed set is uniformly continuous. Thus Lf is uniformly continuous for any $f \in K$. Obviously $Lf \equiv 0$ when $f \equiv 0$, so that L maps the zero function into K.

Now, let $f \in K$ be some function not identically zero. If we can prove that $Lf(x) > 0$ when $0 < x < l/2$, we will have shown that L maps K into itself.

Let $m(x, \tau)$ denote the integral

$$m(x,\tau) = \int_0^{l/2} \sum_{n=0}^{\infty} e^{-\eta_n D\tau} \frac{\phi_n(x)}{||\phi_n||^2} \phi_n(\xi) e^{\frac{-g\xi}{2D}} f(\xi)\, d\xi. \tag{6.4.2}$$

Then $m(x, \tau)$ is a formal solution to Equation (6.2.6), with initial conditions

$$m_0(x) = \begin{cases} f(x)e^{\frac{-gx}{2D}}, & 0 \le x \le l/2, \\ 0, & l/2 < x \le l. \end{cases}$$

That is, the solution to Equation (6.2.6), with initial conditions $m_0(x)$ prescribed above, must be of the form given in Equation (6.4.2).

We shall show that given non-negative initial conditions (not identically zero), we will have $m(x, T_S) \ge 0$ for all $x \in [0, l]$ with $m(x, T_S) > 0$ when $0 < x < l$. If we can show this then, since

$$Lf(x) = e^{\frac{gx}{D} - T_S\left(\frac{g^2}{4D} + \mu_S + \lambda\right)} \Gamma(x; \lambda) m(2x, T_S),$$

we will have proved the desired result for the operator L.

We shall show that $m(x, \tau) \ge 0$ for all $(x, \tau) \in [0, l] \times [0, T]$ in two parts:

Part one: Approximation of $m(x, \tau)$ by nicer functions According to Theorem 6.4.4, there exist positive functions $m_k(x)$, $k = 1, 2, 3, \ldots$, which are continuous and piecewise C^∞ in $[0, l]$ such that $m_k(x) \to m_0(x)$ in $L^2[0, l]$ as $k \to \infty$. Let $m_k(x, \tau)$ denote the right hand side of Equation (6.4.2) with $m_0(x)$ replaced by $m_k(x)$. Then by Theorem 6.4.3, the functions $m_k(x, \tau)$ are continuous. Moreover, using Equation (6.4.2) and a generalised Parseval equality, it can be seen that as $m_k(x) \to m_0(x)$ in $L^2[0, l]$ as $k \to \infty$, we have

$$m_k(x,\tau) \to m(x,\tau), \qquad L^2[0,l] \times [0, T_S]$$

as $k \to \infty$.

The functions $m_k(x,\tau)$ satisfy a max/min principle in the region $[0,l] \times [0,T]$ for any $0 < T \leq T_S$, so that the maximum and minimum of $m_k(x,\tau)$ on $[0,l] \times [0,T]$ must occur at either $x = 0$, $x = l$ or $\tau = 0$.

Part two: The sequence of approximations is non-negative Assume, by way of contradiction that $m_k(x,\tau) < 0$ at some point in $[0,l] \times [0,T_S]$. Then $m_k(x,\tau)$ possesses a negative minimum, and this minimum must occur at either $x = 0$ or $x = l$ (since $m_k(x,0) > 0$, $0 \leq x \leq l$). Moreover, since $m_k(x,0)$ is positive and $m_k(x,\tau)$ is continuous in $[0,l] \times [0,T_S]$, there must be some $\tau_0 > 0$ such that either $m_k(0,\tau_0) = 0$ or $m_k(l,\tau_0) = 0$ and $m_k(x,\tau) > 0$ at $x = l$ and $x = 0$ for all $0 \leq \tau < \tau_0$. But then, by the max/min principle, we must have $m_k(x,\tau) > 0$ for all $0 \leq \tau < \tau_0$.

Let $0 \leq \tau \leq T_S$ be fixed. Note that $m_k(x,\tau)$ is not identically zero, since its expression as a Fourier series (by way of Equation (6.4.2)), has non-zero coefficients.

Now, at $\tau = \tau_0$ we have a minimum of $m_k(x,\tau)$ occurring at either $x = 0$ or $x = l$, so that at one of those points we have $m(x,\tau_0) = 0$. Since $m_k(x,\tau)$ is not identically zero for $0 < \tau \leq \tau_0$ we know that $m_k(x,\tau)$ is not identically constant on $0 < \tau \leq \tau_0$. Therefore, by Theorem D.0.6 of Appendix D, that if $m_k(0,\tau_0) = 0$, then $m_{k,x}(0,\tau_0) > 0$ and if $m_k(l,\tau_0) = 0$ then $m_{k,x}(l,\tau_0) < 0$. Either of these cases violates the boundary conditions satisfied by m_k at $x = 0$ and $x = l$:

$$Dm_{k,x}(x,\tau) - \frac{g}{2} m_k(x,\tau)|_{x=0,l} = 0.$$

Therefore, the assumption that $m_k(x,\tau) < 0$ at some point must be incorrect, and we may say that $m_k(x,\tau) \geq 0$ for all $[0,l] \times [0,T_S]$ and $k = 1, 2, \ldots$.

Now, since $m_k(x,\tau)$ is non-negative for $k \geq 1$ and $m_k(x,\tau) \to m(x,\tau)$ in $L^2([0,l] \times [0,T_S])$ as $k \to \infty$, we find that $m(x,\tau)$ is also non-negative.

Finally we shall show that $m(x,\tau)$ is strictly positive for $0 < x < l$ and $0 < t \leq T_S$:

Note that for any $0 < \varepsilon < T_S$ we know that $m(x,\tau)$ is continuous in $[0,l] \times [\varepsilon, T_S]$. Therefore $m(x,\tau)$ satisfies a strong max/min principle in that region ([24], Theorem 4, Section 2.3.3), so that if m attains it's minimum at any point (x,τ_0), other than the on the one of the lines $\tau = \varepsilon$, $x = l$ or $x = 0$, m is constant in the region $[0,l] \times [\varepsilon, \tau_0]$. Letting $\varepsilon \to 0$ shows that m satisfies the same strong max/min principle on $[0,l] \times (0,T_S]$.

Now, as shown above, the minimum value of m is at least zero, so that if $m(x,\tau) = 0$ at any point $0 < x < l$ and $0 < \tau_0 \leq T_S$, $m(x,\tau) = 0$ for all $(x,\tau) \in [0,l] \times (0,\tau_0]$. But $m(x,\tau)$ is never constant and identically zero when f is not identically zero. This is because the Fourier series representation of $m(x,\tau)$ in Equation (6.4.2) has non-zero coefficients in its sum as long as f is not identically zero. Therefore $m(x,T_S)$ must be greater than zero when $x \in (0,l)$, $0 < t \leq T_S$. This proves the desired result for the operator L.

The proof for L^* is similar: let $m(x,T_S)$ be given by

$$m(x,\tau) = \int_0^l \sum_{n=0}^{\infty} \frac{1}{2}\Gamma\left(\frac{\xi}{2};\lambda\right) e^{-\eta_n D\tau} \frac{\phi_n(x)}{||\phi_n||^2}\phi_n(\xi) e^{\frac{g\xi}{2D}} f(\xi/2)\ d\xi.$$

Then $L^* f(x) = e^{-\frac{gx}{2D} - T_S\left(\frac{g^2}{4D}+\mu_S+\lambda\right)} m(x,T_S)$. Procede as in the case for L. $\square$

Now, the boundary of K consists of all functions in $C[0,l/2]$ which are zero at some point. Thus assuming $\lambda > -\mathcal{M}$, we may conclude from the last theorem that the operators L and L^* *almost* map K (minus the zero function) into its interior (the interior of K consisting of strictly positive, continuous functions on $[0,l/2]$). That is, they map any function in K to one which is strictly positive in $(0,l/2)$, but may be zero at the points $x = 0$ or $x = l/2$. The next theorem shows that the operators do, in fact, map non-zero functions in K into its interior.

Theorem 6.4.5. *When $\lambda > -\mathcal{M}$, the operators L and L^* map non-negative functions in $C[0,l/2]$ (which aren't identically zero to strictly positive functions on $[0,l/2]$. That is, L and L^* map $K\backslash\{0\}$ into its interior.*

Proof. Let $m(x,\tau)$ be defined as in Equation (6.4.2), so that m solves (6.2.6) and

$$Lf(x) = e^{\frac{gx}{D} - T_S\left(\frac{g^2}{4D}+\mu_S+\lambda\right)}\Gamma(x;\lambda) m(2x,T_S),$$

for any $f \in K$.

We showed at the end of the proof of Theorem 6.4.2 that $m(x,\tau)$ was strictly positive for $0 < x < l$, $0 < \tau \leq T_S$. Therefore we find that $m(x,\tau)$ is not identically constant over $x \in [0,l]$ for any fixed τ. If it were, then $m(0,\tau)$ would be positive, but $m_x(0,\tau)$ would be zero, due to $m(x,\tau)$ being constant over $x \in [0,l]$. But then this would violate the boundary condition for m:

$$Dm_x(0,\tau) - \frac{g}{2}m(0,\tau) = 0.$$

Thus, from Theorem D.0.6 of Appendix D, we find that if $m(0,\tau) = 0$ (which implies that $(0,\tau)$ is a minimal point for m) for some $\tau > 0$, then $m_x(0,\tau) > 0$. But the boundary conditions for $m(x,\tau)$ require that

$$m_x(0,\tau) = \frac{g}{2D}m(0,\tau) = 0.$$

Thus, $m(x,\tau)$ cannot be zero at any point $x = 0$, $\tau > 0$.

Similarly, and again by Theorem D.0.6, we find that if $m(l,\tau) = 0$ for some point $\tau > 0$, then $m_x(l,\tau) < 0$. But the boundary conditions for $m(x,\tau)$ require that

$$m_x(l,\tau) = \frac{g}{2D} m(l,\tau) = 0.$$

Thus, $m(x,\tau)$ cannot be zero at any point $x = l$, $\tau > 0$.

We already know that $m(x,\tau)$ is strictly positive for $0 < x < l$, $0 < \tau \leq T_S$. So that we have just shown that $m(x,\tau)$ is strictly positive for $0 \leq x \leq l$, $0 < \tau \leq T_S$.

We therefore find that $Lf(x)$ is strictly positive for $0 \leq x \leq l/2$.

The proof is similar for L^*. □

Now, since L and L^* are compact (by Theorem 6.4.1) and map non-zero functions in K into its interior (by Theorem 6.4.5) we find that L and L^* satisfy the second part of the Krein-Rutman Theorem, (Theorem 5.6.2). Thus we have the following result:

Theorem 6.4.6. *Assume $\lambda > -\mathcal{M}$. Then the operators L and L^*, from $C[0,l/2]$ into $C[0,l/2]$, have a common principal eigenvalue $\nu(\lambda) > 0$ depending on λ. The eigenvalue $\nu(\lambda)$ is simple and the eigenfunctions of L and L^* corresponding to $\nu(\lambda)$ are positive except on a set of zero measure. Moreover, the eigenfunctions are uniformly continuous since L and L^* map bounded sets of functions to equicontinuous sets.*

We now prove that L is continuously dependent on λ, so that we may apply Theorem 5.6.7 in order to show that $\nu(\lambda)$ varies continuously with λ.

Theorem 6.4.7. *L varies continuously with λ when $\lambda > -\mathcal{M}$.*

Proof. Take any $f \in C[0,l/2]$ with $||f|| = 1$ (so that $\sup_{x\in[0,l/2]} |f(x)| = 1$) and let λ, $\lambda' > -\mathcal{M}$. Then, using Equation (6.2.13) and the Cauchy-Schwarz inequality, we find that

$$|L(\lambda)f(x) - L(\lambda')f(x)| \leq \sqrt{\frac{l}{2}} e^{\frac{gx}{D} - T_S\left(\frac{g^2}{4D}+\mu_S\right)} \sum_{n=0}^{\infty} \frac{|\phi_n(2x)|}{||\phi_n||} e^{-\eta_n D T_S} \left| e^{-T_S\lambda}\Gamma(x;\lambda) - e^{-T_S\lambda'}\Gamma(x;\lambda')\right|.$$

Using the definition,

$$\sigma(x) = \sum_{n=0}^{\infty} e^{-\eta_n D T_S} \frac{|\phi_n(2x)|}{||\phi_n||},$$

from Theorem 6.4.1, and recalling that $\sigma(x)$ is continuous on the interval $[0,l/2]$, it can be seen that

$$|L(\lambda)f(x) - L(\lambda')f(x)| \leq \sqrt{\frac{l}{2}} e^{\frac{gx}{D} - T_S\left(\frac{g^2}{4D}+\mu_S\right)} \sigma(x) \left| e^{-T_S\lambda}\Gamma(x;\lambda) - e^{-T_S\lambda'}\Gamma(x;\lambda')\right|.$$

Now, as long as $\lambda > -\mathcal{M}$, the function $\Gamma(x;\lambda)$ is continuous with respect to λ uniformly over all $0 \le x \le l/2$ (the assumption that $\lambda > -\mathcal{M}$ guarantees the continuous dependence on λ of the integrals in the expression for $\Gamma(x;\lambda)$).

Thus, for any $\lambda > -\mathcal{M}$ and $\varepsilon > 0$, there exists some $\delta > 0$ such that when $|\lambda - \lambda'| \le \delta$, we have

$$|L(\lambda)f(x) - L(\lambda')f(x)| < \varepsilon,$$

for all $x \in [0, l/2]$. This implies that $||L(\lambda) - L(\lambda')|| \le \varepsilon$ when $|\lambda - \lambda'| \le \delta$.

This shows that the operator L varies continuously with λ when $\lambda > -\mathcal{M}$. $\square$

The above result shows that, L varies continuously with λ. We can therefore use Theorem 5.6.7 to conclude that $\nu(\lambda)$ varies continuously with λ when $\lambda > -\mathcal{M}$.

We can show a similar result for the operator L^*, but this is not needed since we have already know that L and L^* share the common principal eigenvalue $\nu(\lambda)$. Thus, we only need to apply Theorem 5.6.7 to one of the operators to ensure that $\nu(\lambda)$ varies continuously with λ.

6.5 Sufficient conditions for the existence of a SASD

In the previous section, we found that, under the assumption that $\lambda > -\mathcal{M}$, L has a principal eigenvalue $\nu(\lambda)$ which varies continuously with λ. For a SASD to exist there must be some point where $\nu(\lambda) = 1$. Thus, we require that there exists λ_1 and λ_2 satisfying λ_1, $\lambda_2 > -\mathcal{M}$, such that $\nu(\lambda_1) \ge 1$ and $\nu(\lambda_2) < 1$.

If the existence of λ_1 and λ_2 are shown, then there exist solutions to the Fredholm integral equations (6.2.13) and (6.3.11) for some λ between λ_1 and λ_2. Thus we obtain $S(x,0)$ and $S^*(x,0)$ of our SASD/dual SASD pair. The functions $S(x,\tau)$ and $S^*(x,\tau)$ then evolve with τ according to forward or backward heat equations and therefore they will be non-negative by the max/min principle (this is a similar result to Theorem 6.4.2 and has a similar proof). In fact, the functions $S(x,\tau)$ and $S^*(x,\tau)$ should be strictly positive for $0 < \tau \le T_S$ and $0 \le \tau < T_S$ respectively, by similar reasoning to that used in Theorem 6.4.5.

We then obtain $G_1(x,\tau)$, $G_2(x,\tau)$, $G_1^*(x,\tau)$ and $G_2^*(x,\tau)$ from equations presented in Section 6.2 and 6.3, which, due to the positivity of S and S^*, turn out to be non-negative for $0 \le x \le l$ and $\tau \ge 0$. It can also be checked that, since $\lambda > -\mathcal{M}$, each component of the SASD is in $L^1([0,l] \times [0,\infty))$, while each component of the dual SASD, apart from $S^*(x,\tau)$, is in $L^\infty([0,l] \times [0,\infty))$.

The existence of a point λ_2 such that $\nu(\lambda_2) < 1$ is relatively easy to show. We merely need to note that as $\lambda \to \infty$, $\Gamma(x;\lambda) \to 0$ uniformly on the interval $x \in [0, l/2]$. Thus $||L|| \to 0$ as $\lambda \to \infty$, which in turn implies that $\nu(\lambda) \to 0$ as $\lambda \to \infty$. Therefore there exists some $\lambda_2 > 0$ such that $\nu(\lambda_2) < 1$.

Only one point remains, then, to show that there exists an SASD for some $\lambda > -\mathcal{M}$: we must show that there exists some $\lambda_1 > -\mathcal{M}$, such that $\nu(\lambda_1) \geq 1$. This is a problem that still needs to be addressed in the general case.

Here we shall only deal with an example where k_{G_1}, μ_{G_1} and k_{G_2}, μ_{G_2} are positive constants.

6.5.1 An example

Assume that k_{G_1}, μ_{G_1} and k_{G_2}, μ_{G_2} are positive constants. This implies that $\Gamma(x;\lambda)$ (defined in Equation 6.2.12) is independent of x. We thus write

$$\Gamma(x;\lambda) = \Gamma(\lambda).$$

Moreover, in this case

$$\mathcal{M} = \min\{k_{G_1} + \mu_{G_1},\ k_{G_2} + \mu_{G_2}\}.$$

We then find that $\Gamma(\lambda) \to \infty$ as $\lambda \to -\mathcal{M}^+$. Therefore there exists some $\lambda_1 > -\mathcal{M}$ such that $\nu(\lambda_1) > 1$. Now, take any $\lambda > -\mathcal{M}$. Then there exists a principal eigenvalue $\nu(\lambda)$ of the operator L defined in (6.2.13) with corresponding normalised eigenfunction f. Due to the fact that Γ is independent of x, when we change λ, we do not change the principal eigenfunction. As $\lambda \to -\mathcal{M}^+$, $\Gamma(\lambda) \to \infty$, so that we have

$$\max_{x\in[0,l/2]} |Lf(x)| \to \infty,$$

as $\lambda \to -\mathcal{M}^+$. But, since f is an eigenfunction, $\max_{x\in[0,l/2]} |Lf| = \nu(\lambda)$. Therefore there exists some $\lambda_1 > -\mathcal{M}$ such that $\nu(\lambda_1) > 1$. We already know that there exists some $\lambda_2 > \lambda_1$ such that $\nu(\lambda_2) < 1$. Therefore, by the Intermediate Value Theorem, there exists some $\lambda_1 < \lambda < \lambda_2$ such that $\nu(\lambda) = 1$.

6.6 The entropy functional $\mathcal{H}$ and its derivative

We now sketch how the proof of the stability of any SASD $N(x,\tau)$ would proceed:

Assume the existence of an SASD/dual SASD pair $N(x,\tau)$, $\Psi(x,\tau)$ associated with some λ. A sketch of the analysis required to prove that $N(x,\tau)$ is stable shall now be presented.

Let $n(x,\tau,t)$ be a three-component, vector-valued function which solves the problem (6.1.1)-(6.1.8). We denote the phases of n by the subscripts G_1, G_2 and S, so that, for example, $n_S(x,\tau,t)$ satisfies (6.1.2).

Now, let $m(x,\tau,t) = n(x,\tau,t)e^{-\lambda t}$. We define $\mathcal{H}$ as follows:

$$\mathcal{H}(m|N,\Psi)(t) = \sum_p \int_0^l \int_0^\infty \Psi_p(x,\tau)N_p(x,\tau)H\left(\frac{m_p(x,\tau,t)}{N_p(x,\tau)}\right)\,d\tau\,dx,$$

where p takes the values G_1, S and G_2 and H is a strictly convex function such that $H''(x) > 0$ for all $x \in \mathbb{R}$. Assuming now that m is nice enough so that we may say

$$\mathcal{H}_t(m|N,\Psi)(t) = \frac{\partial}{\partial t}\mathcal{H}(n|N,\Psi)(t) = \sum_p \int_0^l \int_0^\infty \frac{\partial}{\partial t}\Psi_p(x,\tau)N_p(x,\tau)H\left(\frac{m_p(x,\tau,t)}{N_p(x,\tau)}\right)\,dx\,d\tau,$$

we find, by a very messy calculation, that

$$\mathcal{H}_t(m|N,\Psi)(t) \le -\int_0^l \int_0^{T_S} D\Psi_S N_S \left(\frac{\partial}{\partial x}\frac{m_S}{N_S}\right)^2 H''\left(\frac{m_S}{N_S}\right)\,dx\,d\tau \le 0.$$

Since $\mathcal{H}$ is non-negative and it's derivative $\mathcal{H}_t$ is non-positive, we find that $\mathcal{H}$ tends to some limit as $t \to \infty$. Therefore

$$\int_t^{t+T} \mathcal{H}_t(m|N,\Psi)(s)\,ds \to 0$$

as $t \to \infty$. Choosing $H(x) = x^2$, we find that

$$\int_t^{t+T}\int_0^l \int_0^{T_S} \Psi_S(x,\tau)N_S(x,\tau)\left(\frac{\partial}{\partial x}\frac{m_S(x,\tau,s)}{N_S(x,\tau)}\right)^2 dx\,d\tau\,ds \to 0, \qquad t \to \infty.$$

Then, using ideas from Chapter 3 and Chapter 5, it should be possible to use the above convergence result to prove that $n_p(x,\tau,t) \to kN_p(x,\tau)$ as $t \to \infty$ in $L^1_{loc}([0,l]\times[0,\infty))$ for all $p \in \{G_1, S, G_2\}$ where

$$k = \int_0^\infty \int_0^l \Psi^T(x,\tau)n(x,\tau,0)\,dx\,d\tau.$$

6.7 Remaining issues

The sketched analysis in Section 6.6 needs to be carried out in order to show the stability of the SASDs of the model. Further investigation into the general conditions which give $\nu(\lambda)$, the principal eigenvalue of L, greater than one is also needed. If the above points can be addressed, then the asymptotic behaviour of the model in this chapter will be known for quite a range of parameter values.

6.8 Proof of Theorem 6.4.3 and 6.4.4

Proof of Theorem 6.4.3. From a modification of Theorem 6 (suggested below the statement of the theorem), Chapter 9, in [16], we find that when f is specified as in the statement of Theorem

6.4.3, the sum

$$\sum_{n=0}^{\infty} \int_0^l \frac{\phi_n(x)}{||\phi_n||^2} \phi_n(\xi) f(\xi)\ d\xi$$

converges uniformly to f on $[0, l]$. Theorem 1 from Chapter 10 of [17] then shows that

$$\sum_{n=0}^{\infty} \int_0^l e^{-\eta_n D\tau} \frac{\phi_n(x)}{||\phi_n||^2} \phi_n(\xi) f(\xi)\ d\xi$$

converges uniformly over $(x, t) \in [0, l] \times [0, T_S]$. The uniform limit of a sequence of continuous functions is continuous. Therefore the desired result holds. ☐

Proof of Theorem 6.4.4. Let $L^2_+[0, l]$ denote the subset of non-negative functions in $L^2[0, l]$ and let $C^\infty_{++}[0, l]$ denote the subset of strictly positive function in $C^\infty[0, l]$.

From the theorem on page 245 of [38], we find that $C^\infty[0, l]$ is dense in $L^2[0, l]$. Moreover, the subset of non-negative functions in $C^\infty[0, l]$ is dense in $L^{2+}[0, l]$ (See the proof of the aforementioned theorem and the lemma on page 173 of [38]).

Now, let $f \in L^2_+[0, l]$. Then there is a sequence of non-negative functions $f_k \in C^\infty[0, l]$, $k = 1, 2, 3, \ldots$, such that $f_k \to f$ in $L^2[0, l]$ as $k \to \infty$. Define the new sequence of functions $g_k \in C^\infty[0, l]$ as,

$$g_k(x) = f_k(x) + 1/k.$$

Then g_k, $k = 1, 2, 3, \ldots$, is a sequence of functions in $C^\infty_+[0, l]$ tending to f in $L^2[0, l]$. Therefore $C^\infty_{++}[0, l]$ is dense in $L^2_+[0, l]$.

Let us now attempt to modify the functions g_k, $k = 1, 2, \ldots$, so that g_k is piecewise C^∞ in $[0, l]$ and satisfies the boundary conditions specified in the statement of the theorem. We shall modify the functions as follows:

Let $0 < \varepsilon < l/2$ be arbitrarily chosen and take any $k = 1, 2, 3, \ldots$. Let $h_k(x) = g_k(x)$ on the interval $[\varepsilon, l - \varepsilon]$ and let $h_k(0) = g_k(0)$. Define $h_k(x)$ as follows for $0 \le x \le \varepsilon/2$:

$$h_k(x) = g_k(0) + \frac{gx}{2D} g_k(0), \qquad 0 \le x \le \varepsilon/2,$$

so that h_k satisfies

$$D h_k'(0) - \frac{g}{2} h_k(0) = 0.$$

Now, let

$$h_k(x) = \frac{2}{\varepsilon} \left[g_k(0) + \frac{g\varepsilon}{4D} g_k(0) \right] (\varepsilon - x) + \frac{2}{\varepsilon} g_k(\varepsilon)(x - \varepsilon/2),$$

so that $h_k(\varepsilon) = g_k(\varepsilon)$ and $h_k(x)$ is continuous for $0 \le x \le \varepsilon$. Performing a similar construction for $l - \varepsilon \le x \le l$, we obtain

$$h_k(x) = g_k(l) - \frac{g(l - x)}{2D} g_k(l),$$

for $l-\varepsilon/2 \leq x \leq l$, and

$$h_k(x) = \frac{2}{\varepsilon} g_k(l-\varepsilon)(l-\varepsilon/2-x) + \frac{2}{\varepsilon}\left[g_k(l) - \frac{g\varepsilon}{4D} g_k(l)\right](x-l+\varepsilon),$$

for $l-\varepsilon \leq x \leq l-\varepsilon/2$. Thus h_k satisfies

$$Dh_k'(l) - \frac{g}{2}h_k(l) = 0; \qquad h_k(l-\varepsilon) = g_k(l-\varepsilon),$$

and is continuous for $l-\varepsilon \leq x \leq l$.

We have now constructed $h_k(x)$ such that $h_k(x)$ is continuous over all $[0,l]$ and piecewise C^∞ on $[0,l]$, with finitely many jumps in its derivatives. Choosing ε small enough guarantees that h_k is positive. Further $h_k(x)$ and $g_k(x)$ only differ on the intervals $[0,\varepsilon]$ and $[l-\varepsilon,l]$. On the interval $[0,\varepsilon]$ we have

$$\max_{x\in[0,\varepsilon]} |h_k(x) - g_k(x)| \leq \max_{x\in[0,\varepsilon]} g_k(x) + \max_{x\in[0,\varepsilon]} h_k(x). \tag{6.8.1}$$

And, from the construction for $h_k(x)$, as a two-piece linear spline on $[0,\varepsilon]$, we find that

$$\max_{x\in[0,\varepsilon]} h_k(x) = \max\{g_k(0), g_k(0) + \frac{g\varepsilon}{4D} g_k(0), g_k(\varepsilon)\}.$$

Choosing ε small enough then gives

$$\max_{x\in[0,\varepsilon]} h_k(x) \leq 2 \max_{x\in[0,\varepsilon]} g_k(x).$$

Substituting this into Equation (6.8.1), we find that

$$\max_{x\in[0,\varepsilon]} |h_k(x) - g_k(x)| \leq 3 \max_{x\in[0,\varepsilon]} g_k(x) \leq 3 \max_{x\in[0,l]} g_k(x). \tag{6.8.2}$$

Similarly, we may choose ε small enough such that

$$\max_{x\in[0,l]} |h_k(x) - g_k(x)| \leq 3 \max_{x\in[0,l]} g_k(x)$$

holds at the same time as (6.8.2).

Let $\delta = 3\max_{x\in[0,l]} g_k(x)$, then since $h_k(x) = g_k(x)$ when $\varepsilon \leq x \leq l-\varepsilon$, we find that for ε small enough:

$$||h_k(x) - g_k(x)||_{L^2[0,l]} \leq 2\varepsilon\delta^2.$$

Now, for each h_k, let ε be small enough such that $2\varepsilon\delta^2 < 1/k$. Then $h_k(x) \to g_k(x)$ in $L^2[0,l]$ as $k \to \infty$. Since $g_k(x) \to f(x)$ in $L^2[0,l]$ as $k \to \infty$, we find that $h_k(x) \to f(x)$ in $L^2[0,l]$ as $k \to \infty$.

Thus we have constructed a sequence of functions, $0 < h_k(x)$, $k = 1, 2, 3 \ldots$, which are continuous on $[0, l]$ and piecewise C^∞ on $[0, l]$ (with a finite number of discontinuities in its derivatives), such that

$$h_k(x) \to f(x), \qquad L^2[0, l],$$

as $k \to \infty$. Since $f(x)$ was an arbitrary function in $L^2[0, l]$ we have thus shown that the set of positive continuous functions on $[0, l]$, which are piecewise C^∞ on $[0, l]$, is dense in the subset of non-negative functions in $L^2[0, l]$ $\square$

Chapter 7

Discussion and suggestions for further work

We have discussed a variety of problems related to the asymptotic behaviour of some cell-growth models.

In specific instances we have shown asymptotic stability of the steady size-distributions (or steady age-distributions) of the models (Chapter 3 and Chapter 5). We have taken the idea of general relative entropy from [48] and [49], and applied the idea to multi-compartment models in Chapter 5 and Chapter 6. Moreover, we have analysed the behaviour of the general relative entropy functional when dispersion is present in the single-compartment model (Chapter 3).

We began by investigating the behaviour of an instance of the single-compartment model (from Chapter 1, Section 1.4) with $D = 0$ in Chapter 2, and relating the behaviour in that case to the SSDs of the same model with D small and non-zero.

In Chapter 3, an analysis was carried out of the single-compartment model with non-zero D and fixed-size cell division. We found that the Steady-Size distributions of the model, described in [6], are globally asymptotically stable. It was explained at the end of Chapter 3 how the analysis within could be applied to other cases of the single-compartment cell-growth model.

In Chapter 4 a general problem was investigated which was related to the existence of SSDs of the single-compartment cell-growth model. It was found that the existence of 'upper' and 'lower' solutions to a type of nonlocal differential equation implies the existence of a solution which lies between the upper and lower solutions. A recent addition to the work in that chapter allows the inclusion of functional terms such as

$$\int_I b(x,\xi)y(\xi)\ d\xi,$$

in the differential equation, where I is the interval on which the differential equation is solved.

In Chapter 5 we showed stability of a multi-comparment age-distribution model of cell-growth, with periodic birth and death coefficients, assuming the existence of periodic solutions. Theorem 5.4.5 shows that when a (strictly positive) periodic solution exists it is a global attractor (in the sense that the initial conditions of the model do not matter). We also found sufficient conditions for the existence of periodic solutions to the age-distribution model in Chapter 5. We had to draw on the Krein-Rutman Theorem (Theorem 5.6.2) and a functional analysis result from Kato [40] (Theorem 5.6.7).

An outline analysis is given in Chapter 6 for a model based on one in [3, 4]. We apply the Krein-Rutman Theorem and Theorem 5.6.7 to prove the existence of steady age-size distributions to this multi-compartment model. The application of the general relative entropy functional to prove stability of the steady age-size distributions is also discussed briefly.

Future work

A general formula or estimate for the SSDs of the single-compartment model with variable $B(x)$ (cell-division rate) and other coefficients is yet to be found. If such a formula could be found (as well as a corresponding formula for the dual SSD), then a similar analysis to that in Chapter 3 could be performed to show stability of the single-compartment model in those cases.

The recent addition, in Chapter 4, of results pertaining to ordinary differential equations with such terms as

$$\int_I b(x,\xi)y(\xi)\ d\xi,$$

leaves open the possibility of further investigation into equations of this nature. However, since the results in Chapter 4 rely on the existence of upper and lower solutions, it would be convenient to have a set of sufficient conditions for the existence of upper and lower solutions, or some sort of a method to prove the existence of upper and lower solutions in certain cases. The upper and lower solutions in the example in Chapter 4 were constructed heuristically, and so there is not much that can be taken from the example and applied to a general setting.

The work in Chapter 6 is not complete, although a path for further analysis has been laid. Section 6.6, regarding the stability of SASDs contains the least complete part of the work of Chapter 6.

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Appendix A

Compact Operators

A compact operator L on a Banach space X is an operator such that for any bounded sequence $f_n \in X$, $n = 1, 2, 3, \ldots$, the transformed sequence Lf_n, $n = 1, 2, 3\ldots$ contains a convergent subsequence in X [40]. Essentially this means that for any bounded subset $B \subset X$, the closure of LB is compact.

In this thesis we prove compactness of operators in Chapters 5 and 6 using the Arzela-Ascoli Theorem. This theorem is first used in Chapter 4. Before we restate the theorem below, we need to recall what it means for a sequence of functions to be uniformly bounded and equicontinuous. (Everything below is contained in Chapter 4.)

Let $|\cdot|$ be any norm on $\mathbb{R}^d$. The definitions of 'uniformly bounded' and 'equicontinuous' are given, relative to the norm $|\cdot|$, as follows:

Uniformly Bounded: Let $A \subset \mathbb{R}^d$ for some positive integer d and let F be a set of functions mapping $\mathbb{R}^d$ to $\mathbb{R}^d$. The set of functions F is called *uniformly bounded* on A if there exists some $M > 0$ such that $|f(x)| \leq M$ for all $f \in F$ and $x \in A$.

Equicontinuous: The set of functions F is called *equicontinuous* on A if for any $\varepsilon > 0$ there exists a $\delta > 0$ such that $|f(x) - f(y)| \leq \varepsilon$ when $x, y \in A$ and $|x - y| \leq \delta$ for all $f \in F$.

Note that if a set of functions is equicontinuous, then from the above definition we see that each function in the set is uniformly continuous.

The Arzela-Ascoli Theorem: *On a compact set $E \subset \mathbb{R}^d$, let $f_1(y), f_2(y), \ldots$ be a sequence of functions which is uniformly bounded and equicontinuous on E. Then there exists a subsequence* *of functions which is uniformly convergent on E to a limit function $f(y)$.*

Thus, if we have some set of functions $f : E \to \mathbb{R}^d$ in some Banach space X and we desire to know whether the linear transform $L : X \to X$ is compact, we can attempt to show that L maps bounded sequences in X to uniformly bounded and equicontinuous sequences of functions. Using the Arzela-Ascoli theorem should then show that L is a compact operator.

Appendix B

Dual Systems

In Chapters 3, 5 and 6, we use the idea of Dual Systems from [43]. We present the appropriate definitions here for convenience, as well as a result which we use in Chapter 5 and 6 regarding adjoint compact operators on dual systems.

Definition B.0.1. *Let X and Y be linear spaces. A mapping $\langle \cdot, \cdot \rangle : X \times Y \to \mathbb{C}$ is called a* bilinear form *if*

$$\langle \alpha_1 \varphi_1 + \alpha_2 \varphi_2, \psi \rangle = \alpha_1 \langle \varphi_1, \psi \rangle + \alpha_2 \langle \varphi_2, \psi \rangle,$$
$$\langle \varphi, \beta_1 \psi_1 + \beta_2 \psi_2 \rangle = \beta_1 \langle \varphi, \psi_1 \rangle + \beta_2 \langle \varphi, \psi_2 \rangle,$$

for all $\varphi_1, \varphi_2, \varphi \in X$, $\psi_1, \psi_2, \psi \in Y$ and $\alpha_1, \alpha_2, \beta_1, \beta_2 \in \mathbb{C}$. The bilinear form is called nondegenerate *if for every $\varphi \in X$ with $\varphi \neq 0$, there exists $\psi \in Y$ such that $\langle \varphi, \psi \rangle \neq 0$; and for every $\psi \in Y$ with $\psi \neq 0$, there exists $\varphi \in X$ such that $\langle \varphi, \psi \rangle \neq 0$.*

Definition B.0.2. *Two normed spaces X and Y equipped with a nondegenerate bilinear form $\langle \cdot, \cdot \rangle : X \times Y \to \mathbb{C}$ are called a* dual system *and this system is denoted by $\langle X, Y \rangle$.*

Definition B.0.3. *Let $\langle X_1, Y_1 \rangle$ and $\langle X_2, Y_2 \rangle$ be two dual systems. Then two operators $A : X_1 \to X_2$ and $B : Y_2 \to Y_1$ are called* adjoint *(with respect to these dual systems) if*

$$\langle A\phi, \psi \rangle = \langle \phi, B\psi \rangle$$

for all $\phi \in X_1$, $\psi \in Y_2$, where the same symbol, $\langle \cdot, \cdot \rangle$, has been used for the bilinear forms on $\langle X_1, Y_1 \rangle$ and $\langle X_2, Y_2 \rangle$.

We now state a theorem which has implications for the spectrum of two compact adjoint operators. The theorem below appears as Theorem 4.13 in [43].

Theorem B.0.4. *Let $\langle X, Y \rangle$ be a dual system and $A : X \to X$, $B : Y \to Y$ be compact adjoint operators. Then the nullspaces of the operators $I - A$ and $I - B$ have the same finite dimension.*

Immediately this leads to the conclusion that A and B have the same non-zero eigenvalues. Since for any eigenvalue $\lambda \neq 0$ of A we know that $\frac{A}{\lambda}$ is compact, with adjoint operator $\frac{B}{\lambda}$. Therefore the nullspaces of $I - \frac{A}{\lambda}$ and $I - \frac{B}{\lambda}$ have the same finite dimension. Thus λ is also an eigenvalue of B.

Appendix C

Jensen's Inequality

Definition C.0.5. *Let $U \subset \mathbb{R}$. A function $H : \mathbb{R} \to \mathbb{R}$ is called* convex *on U if, for any $x, y \in U$,*

$$H(\lambda x + (1-\lambda)y) \leq \lambda H(x) + (1-\lambda)H(y)$$

for all $0 \leq \lambda \leq 1$. The function H is strictly convex *if*

$$H(\lambda x + (1-\lambda)y) < \lambda H(x) + (1-\lambda)H(y)$$

for all $0 < \lambda < 1$.

In this thesis, whenever we refer to convex functions, we mean twice continuously-differentiable convex functions on $\mathbb{R}$. So that $H''(x) \geq 0$ for all $x \in \mathbb{R}$.

Let $H : \mathbb{R} \to \mathbb{R}$ be a convex function. Then for any $\Omega \subset \mathbb{R}$, we have Jensen's inequality:

$$\int_\Omega H(f(x))\ d\mu(x) \geq H\left(\int_\Omega f(x)\ d\mu(x)\right),$$

where

$$d\mu(x) = p(x)dx,$$

for some probability density function $p(x)$ on Ω and f is a function from Ω into $\mathbb{R}$ such that f and $H \circ f$ are μ-integrable. If $H(x)$ is chosen such that $H''(x) > 0$ for all $x \in \mathbb{R}$ (note that this implies that H is strictly convex), then equality only holds when $f(x)$ is a constant except on a set of μ-measure zero. In fact, in [19], it is stated that this strict equality result will hold as long as $H(x)$ is not linear on any neighbourhood of $\int_\Omega f(x)\ d\mu(x)$. We shall prove this result now in the case where $H''(x) > 0$ for all $x \in \mathbb{R}$:

When $H''(x) > 0$ for all $x \in \mathbb{R}$, we have

$$H'(x_0)(x - x_0) + H(x_0) \leq H(x),$$

for all x, $x_0 \in \mathbb{R}$, with equality holding only when $x = x_0$. Then letting

$$x_0 = \int_\Omega f(x)\ d\mu(x),$$

we see that

$$H(x_0) = H'(x_0) \int_\Omega f(x)\ d\mu(x) + H(x_0) - H'(x_0)x_0.$$

But since $\int_\Omega d\mu(x) = 1$, we find that

$$H(x_0) = \int_\Omega H'(x_0)[f(x) - x_0] + H(x_0)\ d\mu(x).$$

Now, since $H'(x_0)[f(x) - x_0] + H(x_0) \leq H(f(x))$ when $H''(x) > 0$, with equality holding only when $f(x) = x_0$, we have

$$H\left(\int_\Omega f(x)\ d\mu(x)\right) = H(x_0) \leq \int_\Omega H(f(x))\ d\mu(x),$$

with equality holding only when $f(x) = x_0$ on Ω except for a set of μ-measure zero.

As an example, let $f : [a, b] \to \mathbb{R}$ be a continuous function and let H be some convex function. Then

$$\frac{1}{b-a} \int_a^b H(f(x))\ dx \geq H\left(\frac{1}{b-a} \int_a^b f(x)\ dx\right).$$

See [58] for a general formulation of Jensen's Inequality.

Appendix D

Boundary behaviour of the heat equation

Here we present a theorem, used in the proof of Theorem 3.4.10, Chapter 3 and in the proof of Theorem 6.4.2 and Theorem 6.4.5, Chapter 6. It is stated in a slightly different manner from Theorem 15.4.1 of [13], but has the same proof.

Theorem D.0.6. *Let $u(x,t)$ solve the heat equation in the region $R = (a,b) \times (0,T]$ and be continuous in the region $\overline{R} = [a,b] \times [0,T]$ for some $a < b$ and $T > 0$. Let $0 < t_0 \leq T$.*

If u assumes its maximum on $\overline{R}$ at (b,t_0) and is not identically constant on $[a,b] \times [0,t_0]$, then

$$u_x(b,t_0) > 0,$$

when $u_x(b,t_0)$ exists. If u assumes its minimum at (b,t_0) and is not identically constant on $[a,b] \times [0,t_0]$, then

$$u_x(b,t_0) < 0,$$

when $u_x(b,t_0)$ exists.

Similarly if u assumes its maximum at (a,t_0) and is not identically constant on $[a,b] \times [0,t_0]$, then

$$u_x(a,t_0) < 0,$$

when $u_x(a,t_0)$ exists. If u assumes its minimum at (b,t_0) and is not identically constant on $[a,b] \times [0,t_0]$, then

$$u_x(a,t_0) > 0,$$

when $u_x(a,t_0)$ exists.

Proof. See the proof of Theorem 15.4.1 in [13]. □